UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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OBSTETRICS AND GYNECOLOGY DEVICES PANEL

+ + +

September 24, 2015
8:00 a.m.

FDA White Oak Campus
Building 31 – The Great Room, Room 1503
Silver Spring, Maryland

PANEL MEMBERS:

CHERYL B. IGLESIA, M.D., FACOG	Temporary Chair
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RICHARD J. CHAPPELL, Ph.D.	Non-Voting Member
CHARLES C. CODDINGTON, M.D.	Non-Voting Member
DENISE M. ELSER, M.D., FACOG	Non-Voting Member
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DAVID B. SEIFER, M.D.	Non-Voting Member
PHILLIP G. STUBBLEFIELD, M.D.	Non-Voting Member
MARSHA WILLS-KARP, Ph.D.	Temporary Non-Voting Member
CYNTHIA CHAUHAN, M.S.W.	Consumer Representative
JO-ELLEN DE LUCA	Patient Representative
JAMES GARDNER, M.D., M.B.A.	Industry Representative
SHANIKA CRAIG, M.B.A., M.H.A.	Designated Federal Officer

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Patient

KRYSTAL DONAHUE
Patient

ELENA MENDEZ, RN
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CHANDRA FARMER
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REBECCA HOWELL
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GABRIELLA AVINA, RN, M.S.N., M.B.A.
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CECILIA BOGLE
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SHARILYN ERVIN
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JANIE GARCIA
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RUPAL JURAN, M.D.
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TABATHA ROMERO
Patient

AMANDA HOLT
Patient

SHEILA PITT
Patient

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Patient

ALICIA GREAGER
Patient

KIMBERLY HUGHES
Patient

SUSAN SCANLAN
President, Women's Research and Education Institute

CHRISTINE CERVANTES
Patient

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M E E T I N G

(8:04 a.m.)

DR. IGLESIA: Good morning. I would like to call this meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee to order.

My name is Dr. Cheryl Iglesia. I am the Chair of this Panel. I am director of the section of female pelvic medicine and reconstructive surgery at MedStar Washington Hospital Center and a Professor of Obstetrics and Gynecology and Urology at Georgetown University School of Medicine.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss the risks and benefits of Bayer HealthCare's Essure system for permanent female sterilization. The system, originally approved in November 2002 under P020014, consists of a delivery system and nickel-containing permanent implants. The implants are placed without a skin incision, through the vagina, within each fallopian tube. They elicit tissue ingrowth, which over time results in tubal occlusion.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. I'd like to start to my right with Dr. Gardner. And, please, yeah, hit the red button.

DR. GARDNER: Hi, my name is Jim Gardner. I am the Industry Representative on the

Panel. I'm employed by Cook Medical, which is a family of medical device manufacturers based in Bloomington, Indiana, where I serve as medical science officer and director of reimbursement for the organization.

MS. CHAUHAN: Cynthia Chauhan, Consumer Representative.

MS. DE LUCA: Jo-Ellen De Luca, Patient Representative.

DR. SEIFER: David Seifer, OHSU, reproductive endocrinology.

DR. JANIK: Grace Janik, Reproductive Specialty Center, Milwaukee, reproductive endocrinology and fertility and minimally invasive surgery.

DR. CODDINGTON: Charles Coddington from the Mayo Clinic, Department of Obstetrics and Gynecology, where I am a gynecologic surgeon and reproductive endocrinologist.

DR. CHAPPELL: Rick Chappell, Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison.

DR. MYERS: Dr. Deborah Myers, Professor of OB/GYN at Brown Medical School, Providence, Rhode Island. Expertise is female pelvic medicine and reconstructive surgery.

DR. ELSER: Dr. Denise Elser, female pelvic medicine and reconstructive surgery in the Chicago area.

MS. CRAIG: Shanika Craig, designated federal official.

DR. MILNER: Dr. Josh Milner, Senior Investigator in the National Institute of Allergy and Infectious Diseases; allergy and immunology.

DR. STUBBLEFIELD: Phillip Stubblefield, obstetrician/gynecologist at Beth Israel Deaconess Hospital in Boston, and practice in the division of family planning.

DR. KATZ: David Katz, Duke University. I am a Professor of Biomedical Engineering and a Professor of Obstetrics and Gynecology.

DR. SCHALOCK: Peter Schalock, Harvard Medical School, Mass General Hospital, Associate Professor of Dermatology.

DR. BAIRD: Donna Baird. I'm with the National Institute of Environmental Health Sciences, a reproductive epidemiologist and adjunct professor at the University of North Carolina.

DR. WILLS-KARP: Dr. Marsha Wills-Karp. I'm at the Johns Hopkins School of Public Health. I am a professor in the Department of Environmental Health Sciences, and my area of expertise is allergy and immunology.

DR. YUSTEIN: Ron Yustein. I am the Clinical Deputy Director in the Office of Surveillance and Biometrics at the Center for Devices and Radiological Health here at FDA.

DR. FISHER: Ben Fisher. I'm the Division Director for the Division of Reproductive, Gastro-Renal, and Urological Devices in the Office of Device Evaluation here in the Center for Devices. I am a developmental toxicologist with a focus on developmental genetics.

DR. IGLESIA: Thank you very much. And if you could all just turn off your mikes when you're not speaking and just turn them on when you are, because this is being recorded, for the background noise.

So, for topics being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak

into the record only if recognized by the Chairperson. We look forward to a productive meeting.

Members of the audience, if you have not already done so, please sign the attendance sheets that are located on the registration table directly outside of the meeting room.

And Ms. Shanika Craig, the Designated Federal Officer for the Obstetrics and Gynecology Devices Panel, will now make some introductory remarks.

MS. CRAIG: I will now read the FDA Conflict of Interest Disclosure Statement, Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee, September 24th, 2015.

The Food and Drug Administration is convening today's meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of the Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at U.S. Code 18 Section 208 are being provided to participants today in today's meeting and to the public.

FDA has determined that the members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under U.S. Code 18

Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of U.S. Code 18 Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss the risks and benefits of Bayer HealthCare's Essure system for permanent female sterilization. This system, approved in November 2002, consists of a delivery system and nickel-containing permanent implants. The implants are placed without a skin incision, through the vagina, within each fallopian tube. They elicit tissue ingrowth, which over time results in tubal occlusion.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and the consultants, no conflict of interest waivers have been issued in accordance of U.S. Code 18 Section 208.

Dr. James Gardner is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Cook, Incorporated.

We would like to remind members and consultants that if the discussion involves any

other products or firms not already on the agenda for which FDA participants have a personal or imputed financial interest, that participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during the meeting and will be included as a part of the meeting official transcript.

For the duration of the Obstetrics and Gynecology Devices Panel meeting on September 24th, 2015, Ms. Jo-Ellen De Luca has been appointed to serve as a Temporary Non-Voting Patient Representative, and Dr. Marsha Wills-Karp has been appointed to serve as a Temporary Non-Voting Member. For the record, Ms. De Luca serves as a consultant to the Gastrointestinal Drugs Advisory Committee in the Center for Drug Evaluation and Research, and Dr. Wills-Karp serves as a consultant to the Allergenic Products Advisory Committee in the Center for Biologics Evaluation and Research. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

These appointments were authorized by Jill Hartzler Warner, J.D., Associate Commissioner for Special Medical Programs, on September 22nd, 2015.

Before I return the meeting back over to Dr. Iglesia, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone number (410) 974-0947.

Information on purchasing videos of today's meeting and handouts for today's presentations are available at the registration table outside of the meeting room.

The FDA press contact for today's meeting is Deborah Kotz.

All written comments received were provided to the Panel for their review prior to today's meeting. The link to the docket, which contains the written comments, is available at the registration table.

I would like to remind everyone that the members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to the FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session and have not previously provided an electronic copy of your slide presentation to the FDA, or it has changed, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you.

Dr. Iglesia.

DR. IGLESIA: Thank you, Ms. Craig.

We will begin today's meeting with introductory remarks from the Assistant Commissioner for Women's Health, Marsha Henderson.

MS. HENDERSON: Good morning. I am Marsha Henderson, Assistant Commissioner

for Women's Health. The Office of Women's Health is responsible for protecting and advancing the health of women through policy, science, and outreach.

Thank you for coming to the FDA to participate in this important public Advisory Committee meeting. All FDA Advisory Committee meetings are centered in science, and this one will be as well. But the FDA also called this meeting because we value your point of view, and we want to hear your very personal and professional perspectives. We are committed to being transparent and sharing information with the public. We know that it is critical to listen to the voices of patients, advocates, health professionals, and companies throughout the lifespan of the products we regulate. The Agency's primary concern is the safety and well-being of patients.

FDA's product review centers carefully monitor all reports of potential harms. They review a variety of sources to get as full a picture as possible of how devices work in the real world after approval. This means examining adverse reports submitted, reviewing the scientific data that manufacturers submit to FDA annually, reading the scientific literature, speaking to the clinicians who are using our regulated devices, and reviewing the public comments on the dockets for meetings like this one. Although the Office of Women's Health has no direct regulatory authority, we support these efforts. And we know that as the science evolves, so will the Agency's science-based decisions, as we carefully weigh each product's benefits and risks.

Over the years FDA's human product centers, like the Center for Devices and Radiological Health, have placed greater emphasis on the health needs of women and greater emphasis on the collection of data on women who participate in clinical trials.

These efforts have resulted in the development of new guidance and regulations for industry, advances in women's health research, outreach to communicate risk information to women, more detailed information on product safety and effectiveness when used on women, and of course, the approval of many lifesaving products.

I want to end by saying that I applaud the effort CDRH has made in preparation for this public meeting. It offers patients, members of the public, and healthcare providers with an opportunity to present their positions and for us to hear their concerns. We are listening.

Again, thank you for coming today to share your --

(Microphone off.)

DR. IGLESIA: Thank you, Assistant Commissioner Henderson.

At this time we will hear a presentation by Bayer HealthCare. I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Bayer HealthCare, you may begin.

DR. ZAMPAGLIONE: Thank you, Madam Chairperson, members of the Committee, FDA, and members of the public. We are grateful for this opportunity to work with the Committee to review the benefits and risks of Essure.

Good morning, everyone. My name is Dr. Edio Zampaglione. I am the Vice President for U.S. Medical Affairs for Women's Healthcare and Neurology. Prior to joining the pharmaceutical industry, I was a private practitioner OB/GYN. I cared for many patients like the women here today who are to speak and tell their story. I learned a lot about what they

go through, their concerns, and how important it is that they are listened to and that their concerns are properly addressed. Our number one priority at Bayer is ensuring patient safety through the appropriate use of our products. We welcome the opportunity for an ongoing and open dialogue on permanent birth control and look forward to working closely with the FDA on any next steps that are discussed at this meeting.

So our presentation this morning will have several sections. I will present the clinical need for permanent birth control options, followed by a brief overview of Essure, the clinical development program and the physician training program. I will then conclude my portion of the presentation with a review of the topics of interest as identified by the FDA. Dr. Cindy Basinski, a private practitioner in Indiana with extensive experience in the placement and the management of Essure, will describe the need for permanent birth control as well as her experience as an Essure provider. Dr. Patricia Carney, Director of U.S. Medical Affairs for Women's Health at Bayer, will finish up the presentation with a review of the benefit-risk summary for Essure.

So data from the 2011 to 2013 National Survey of Family Growth has demonstrated that about 45% of women age 25 to 44 years old, who have completed childbearing, use permanent birth control as their method of contraception. That equates to about 650,000 procedures a year. About half of them are done as what's known as interval procedures, which means they are performed at a time that's distant from childbirth.

Now, prior to the approval of Essure, women had only one option, and that was a laparoscopic bilateral tubal ligation or a tubal ligation done through an open incision called a laparotomy. Now, while these procedures are common and relatively simple to perform,

they are not without risks, and some of them can have serious consequences. So it was recognized that there was a need for an alternative approach to permanent birth control. Approval of the Essure system in 2002 made an alternative approach to permanent birth control possible by providing women with an important option so that they can achieve their personal reproductive objectives.

The Essure system is a Class III PMA device. It was approved by the FDA on November 4th, 2002, following the PMA review pathway. Now, this pathway is the most stringent FDA review process for devices prior to marketing.

Essure is commercially available in the United States, Canada, a number of European countries, Australia, and several Latin American and Asian Pacific countries. Since its approval, approximately 1 million Essure systems have been distributed worldwide.

The Essure system is indicated for women who desire permanent birth control by bilateral tubal occlusion of the fallopian tubes. The inserts are small and flexible. They're approximately 4 cm in length and expand up to about 2 mm when released from the delivery catheter. The device is only to be used by physicians who are knowledgeable hysteroscopists and have successfully completed the mandatory training program.

So let's watch an animation of a placement. As you can see, the inserts are fed into the fallopian tubes through a delivery catheter. They are released from the delivery catheter on both sides. Once placed, occlusion takes about 3 months to occur. During this 3-month period, the patient must use an alternate method of contraception until the required 3-month confirmation test documents appropriate location and occlusion. If the inserts are found to be in the proper location, there's a very high likelihood, approximately

99%, that occlusion will have occurred. Initially, the only confirmation test in the United States was the hysterosalpingogram or a modified hysterosalpingogram. Bayer recently received approval for the use of transvaginal ultrasound as a first-line option for the confirmation test if certain criteria during the procedure were met. If the confirmation test is satisfactory, she is told she can rely on Essure and is no longer required to use an alternate method of contraception.

I will now give a brief overview of the Essure clinical development program just to demonstrate how rigorously the Essure device has been and continues to be studied.

The original insert was called the STOP device, and this was used in the registration studies. The feasibility studies were conducted in women who were scheduled to undergo a hysterectomy for benign reasons. The objective of these studies was to demonstrate the feasibility and safety of the Essure placement procedure and to provide support for the mechanism of action.

The Phase II and pivotal studies were multi-center international studies determining the safety and efficacy of Essure. These studies are the basis for the safety and efficacy data that appear in the instructions for use and met all requirements for a Class III device. In fact, since it was a first-of-a-kind device, the FDA referred the PMA to an outside Panel of experts on July 22nd, 2002. The Panel reviewed and discussed the safety, efficacy, labeling, training, and post-approval requirements. Eight of the nine experts agreed that Essure should be approved, with one abstaining due to personal reasons. As with any medical device, research and development continues to look at incremental refinements to improve safety and performance.

This slide demonstrates the refinements of the Essure system over the course of the development program. The feasibility, Phase II, and pivotal studies used the STOP insert and delivery catheter. The first U.S. launch of the device was the ESS205, which refined the delivery system for the same STOP insert, as shown on the top.

Through direct feedback gathered from physicians, a more user-friendly delivery catheter was developed. This is the currently available Essure system called the ESS305. For this model, minor changes were made to the proximal end of the insert to accommodate changes made to the delivery catheter. You can see that on the left side of the two photos of the inserts. These refinements did not affect the critical design aspects of Essure or the safety and efficacy of the device as demonstrated in the post-approval clinical trials.

The top portion of this slide shows two post-approval studies that continue to evaluate the safety and efficacy of Essure as well as assess the learning curve for physicians. The first study evaluated the minor changes to the delivery catheter from the STOP to the ESS205. The second study evaluated the change of the delivery catheter from the ESS205 to the 305. Both studies evaluated bilateral placement rates with the design changes made to the delivery system, as well as the bilateral placement rate of newly trained Essure physicians versus physicians who were experienced. Placement rate data from the 305 is reflected in the current instructions for use.

These next two studies that are shown are currently ongoing. The transvaginal ultrasound study was conducted to support the use of TVU as a first-line confirmation test in the United States and is currently in the long-term extension phase where patients will

be followed up to 10 years. What is particularly valuable about the TVU study is that the current version of the ESS305 was used. The study demonstrated a safety and efficacy profile that is consistent with the original pivotal study.

The purpose of the last study on this slide is to evaluate the effectiveness and safety of the Essure system when a NovaSure endometrial ablation procedure is performed following a successful Essure confirmation test. This study is expected to be completed in the next few years.

The body of knowledge about the safety and efficacy of Essure continues to grow, and a lot of data also comes from outside of the United States. A large study in France called SUCCES II is currently ongoing with 2,600 women enrolled and being followed long term. SUCCES II is a prospective, non-interventional, multi-center observational study. Recruitment started in 2008, and the primary objective of the study is the assessment of patient satisfaction at 5 years. Secondary objectives include assessment of complications.

Because this is an observational study, there is no systematic collection of safety endpoints, with the exception of the 3-month post-procedure time point. Patients at this time point were specifically asked if they experienced bleeding and/or pain or cramping post-procedure. After the 3-month post-procedure time point, safety data was collected at 1-, 2-, and 5-year contacts where patients were asked if they experienced any adverse events.

This table shows the results focusing on bleeding and pain or cramping reported at the 3-month time point and the interim 2-year assessment. As expected, given the specific questions on post-procedural pain and cramping and bleeding at the 3-month follow-up,

relatively high rates of these symptoms were reported. At subsequent contacts, rates of bleeding and pain were consistent with rates found in other studies. Five pregnancies have been reported, resulting in a contraceptive efficacy rate of approximately 99.6%. And the adverse events reported in the interim analysis as of July 2015 in SUCCES II are similar to the type and frequency to those already identified in the pivotal study.

So data about Essure continues to accrue in clinical trials that further characterize the experience and risks with this device.

So, to summarize the clinical data, a total of 2,676 women have been studied, with 557 completing 5 years of follow-up. And the TVU study follow-up will continue to follow an additional 493 women for 10 years. In addition, SUCCES II has added another 2,600 with 5 years of planned follow-up in an observational study.

As shown, a relatively large number of women are being studied out to 5 and even 10 years, and a consistent efficacy and safety profile has been observed with the clinical data and long-term follow-up. We use this data and experience as part of the Essure physician training program known as the Clinical Pathway.

Now, this program is to train physicians that we have and is regularly updated. The training has been mandatory since the PMA approval in 2002. A physician must successfully complete the Clinical Pathway certification before being able to independently order and perform the Essure procedure.

The Clinical Pathway program has three steps. Step 1 is the didactic portion that provides an overview on Essure, including appropriate patient selection, counseling, indications, contraindications, warnings, precautions, the placement steps and the

confirmation test, and all the clinical trial data available. This basically follows the instructions for use. The physicians also receive a comprehensive training manual as well as a demonstration video of the Essure procedure. Once they complete this first step, they move on to a hands-on training that involves the use of computer simulators and/or silicone uterine models. The final step involves placing Essure in patients under direct supervision and demonstration of proper technique and at least five procedures. Once the Clinical Pathway is completed, the physician receives a certificate of completion.

Now, our commitment to training doesn't stop with the Clinical Pathway. It also includes a physician's office staff such as nurses and other appropriate staff members. The key counseling points are reviewed, and the importance of a patient following all of the necessary steps through the confirmation test are stressed. They also learn where they can find all the resources on the Essure website, and these resources can be downloaded to support patient care.

Several additional physician programs have also been developed over the years. We offer this advanced workshop that is conducted in collaboration with the major endoscopic equipment company and Essure experts. It emphasizes office-based procedures, placement of the Essure inserts in challenging cases, and interpretation of the confirmation test.

Radiologists also play a very important role in the Essure procedure, as they are most often the ones performing the confirmation tests. A training program was implemented to provide radiologists with the information they need to interpret the confirmation test. All three programs I've discussed so far are tailored to the practicing professionals.

Residents are the future practicing physicians, and therefore it is important to provide them the skills to effectively offer Essure to their patients. A program specific for residents was implemented and has been adopted in the majority of OB/GYN residency programs in the United States. The program is led and managed by the residency director or any attending staff that's intimately involved with resident education. In addition to the structured training, we offer a number of individualized support services to address any specific need a physician may have.

The proctor program. This facilitates peer-to-peer placement training with experienced physicians. We have a national consultancy network which consists of physicians with extensive experience in the management of Essure patients. Case-specific questions to Bayer's medical information center are triaged to these consultants.

Physician inquiry requests, or PIRs, are managed by our medical information department and encompass a variety of questions ranging from providing data to triaging guidance on specific issues. These PIRs are recorded, and they're tracked. This gives us the ability to monitor and determine the types of questions physicians are asking. And this then allows us to cross-reference our training curriculum and look for areas that may need to be addressed.

So before I go into the topics of interest and share the data available, I would like to briefly review additional sources of data and information that inform these topics. In our own review document for this meeting, we draw on clinical trial data, external literature, and postmarketing monitoring data to address all of the topics of interest identified for this Advisory Panel meeting.

Regarding the external literature, we have focused on independently conducted and funded studies that appear in peer review journals in order to minimize biases.

And, regarding the postmarketing monitoring, the number of adverse event reports has increased over time, which is reflective of the increased exposure to Essure, as based on the number of kits sold. However, there has been a noticeable increase in case reports since the third quarter of 2013 and a disproportionate increase in non-medically confirmed cases. This increase coincides with the acquisition of Conceptus. And there's also been a recent increase in social media as well as traditional media. But Bayer has responded to these trends with activities that facilitate reporting, such as active listening and subsequent outreach programs to try to obtain as much information as possible and better understand these cases.

As the FDA stated in their review document for this meeting, there are many limitations to postmarketing adverse event reporting. But, despite these limitations, we consider it important to closely analyze the reports and types of adverse events received.

I will now present data on the topics of interest as identified by the FDA. In the interest of time, I will present data on seven of the topics, but all the topics are addressed in our Executive Summary that the Panel has received. The topics I will present today are efficacy; unsatisfactory location; pain, specifically persistent and chronic pain; allergic reaction and hypersensitivity to nickel; device removal; death; and pregnancy outcomes. Whenever possible we will present clinical trial data followed by the literature and postmarketing data. So let's begin with efficacy.

Now, we all know no method of contraception is 100% effective. And, since

approval, the instructions for use and all patient materials have clearly stated that fact. While no pregnancies were reported in the Phase II or pivotal trials, all labeled materials have always stated that pregnancies can occur with Essure in place and have been reported in the commercial setting. In the most recent study supporting the use of transvaginal ultrasound as a first-line confirmation test in the United States, four pregnancies out of 547 subjects were reported. Of the four pregnancies that occurred in the TVU study, two were due to perforations and two were due to unsatisfactory device location.

Several published studies in the United States look at Essure efficacy. Shown here are independently performed and independently funded studies. On this graph, the vertical line represents 99.2% contraceptive efficacy, the overall rate noted from these studies. Overall, a consistent picture of efficacy is seen. Independently performed studies in other countries report the same efficacy rate. The postmarketing reporting frequency of pregnancy is 0.21%, which includes pregnancies occurring before the confirmation test.

So, in conclusion, pregnancies with Essure in place have been reported in the commercial setting and in the literature.

Patient compliance with the 3-month alternate contraception as well as obtaining the confirmation test are important factors to prevent unintended pregnancies.

The findings are consistent across all data points and demonstrate an efficacy of greater than 99% when the Essure device is confirmed to be in the proper place and location.

I will now discuss unsatisfactory location of Essure inserts. Placing the inserts in a proper location is important for efficacy, as I've stated. A properly placed insert spans the

interstitial segment of the fallopian tube. The ultimate location of the tube -- in the tube, I'm sorry, is primarily determined by the position of the insert at the time of deployment in the placement procedure.

Unsatisfactory locations can be divided into three groups. One is when the insert is deployed too proximally or not sufficiently far in the tube, with most of it lying in the uterine cavity. These can be expelled into the uterus or vagina and even out through the body and can be associated with bleeding and/or cramping.

The second unsatisfactory location is when the insert was advanced too far into the tube and is distal from its ideal location.

The third unsatisfactory location is where the insert perforates the tube or uterus, and these perforations can be associated with significant pain or discomfort.

Distally placed inserts or perforations are more likely to migrate or get expelled into the pelvis or abdomen. Migration may occur between the hysteroscopic placement and the confirmation test. But migration of a satisfactorily located insert, as determined by the confirmation test, is unlikely to occur as tissue ingrowth around the device stabilizes its position.

This is the data on the reasons for unsatisfactory locations reported from the clinical trials and the Phase II, pivotal, and the most recent TVU study. The reported ranges for total unsatisfactory location ranged from 2% to 6.5%, as seen in the last column on the right. The range for perforation was 0.3% to 3.4%. The literature contains only a few studies analyzing the rates of unsatisfactory location. They focus primarily on perforation. A review of these studies and cases show that abdominal pain was the most common

symptom reported with perforation, though most are asymptomatic. Perforation and migration rates ranged from 0.02% up to 3.6%. The majority of cases in our postmarketing database are medically confirmed, and the reporting frequency noted for all types of unsatisfactory locations is approximately 0.4%.

In conclusion, unsatisfactory location of an insert is a known complication of the Essure procedure. The warnings and risks regarding an unsatisfactorily located insert are clearly stated in the instructions for use and patient information booklet.

An examination of peer-reviewed published literature and an analysis of all data available reveal that incidence of unsatisfactory location inserts are low.

As an unrecognized unsatisfactorily located insert can have serious consequences, the physician training program emphasizes identification through either the patient symptoms or the confirmation imaging as well as the appropriate management of these cases.

The next topic of interest is persistent and chronic pain. Chronic pelvic pain is a common gynecologic problem with an estimated prevalence between 5.7% and 26.6%. Some transient pain or discomfort is expected with the Essure placement procedure. However, as with any procedure we do in medicine, any patient with unexpected or prolonged pain must be evaluated.

This graph represents the reported incidence of pain during the pivotal trial and 5-year follow-up. Overall, the rates of pain are consistently low and continue to decrease with time.

This slide shows the rates of recurrent and persistent pelvic pain during the pivotal

study and 5-year follow-up. Recurrent pain was defined as pain that was reported at least twice during the follow-up period. Persistent pain is defined as pain that was reported at every prior follow-up visit.

A retrospective study of 458 women found that chronic pain, defined as pain lasting more than 3 months after the procedure, occurred in about 4.2% of women. In a large database review of almost 27,000 patients, 0.88% of women who chose hysteroscopic sterilization and 0.93% of women who chose laparoscopic tubal ligation had a diagnosis of chronic pain post-procedure. Formal testing proved that there was no statistical difference between the two groups. From our postmarketing monitoring, the reporting frequency for abdominal, pelvic, and back pain is 0.3%. Reports on pain from healthcare professionals are frequently reported in the context of unsatisfactory device location.

So, in conclusion, short-term pain or discomfort after the Essure procedure is expected and is reflected in the instructions for use and patient information booklet.

The only comparative study between bilateral tubal ligation and hysteroscopic sterilization reported no difference in pain rates post-procedure.

Analysis of the data reveal that improperly placed Essure inserts have been identified as a potential factor for persistent or chronic pain.

So let's turn to allergic reaction. The development of nickel hypersensitivity and/or allergic reaction is a consideration with a nickel-containing device in situ. However, as with all medical devices, the materials used in Essure are of medical-grade quality as opposed to the nickel contained in everyday items such as jewelry. Essure inserts are made of a super-elastic nitinol outer coil and a stainless steel inner coil wrapped in PET fibers. Since the

mid-'80s, nitinol has reliably been used for medical and dental applications, products such as vascular stents, heart valves, orthodontic archwires, all common nitinol applications. The nickel ions in nitinol are tightly bonded to titanium. The entire alloy surface is covered with a protective layer of titanium oxide. Both the bonding and the protective layer minimize nickel ion release.

In vitro testing of the Essure inserts found that the maximum leaching rate is approximately 0.14 µg/day. Now, this is far less than what is noted from other approved nitinol implantable devices, which can range from 0.42 to 8.4 µg/day. And all of these pale in comparison to the normal daily exposure from food and water, which can be up to 300 µg/day. Furthermore, all biocompatibility testing requirements were met.

Now, allergic reactions to nitinol are rare. Only 3 in more than 5,000 women in company-sponsored studies reported symptoms consistent with an allergic reaction. The peer-reviewed published literature contains few reports on nitinol allergic reactions in general or specifically regarding Essure. A large retrospective study in Spain of over 4,300 women revealed only two cases of allergic reaction to Essure, with a reported rate of 0.05%. And studies have also demonstrated that there's no correlation between skin-testing results and allergic reactions to Essure.

Postmarketing monitoring reports a reporting frequency of suspected allergies. It's approximately 0.06%. Fifteen percent of the reported cases in our database were test or specialist confirmed allergies.

In conclusion, the amount of nickel released from Essure is minimal, hypersensitivity is rare, and clinical trial and published literature support a rate of less than 0.1%.

Skin patch testing is not a reliable predictor of clinically significant reactions to nickel-containing implantable devices. But appropriate counseling is very important prior to implanting inserts.

Let's turn now to device removal. The Essure inserts are intended to be left in place. The instructions for use, however, has always provided guidance about when removal is appropriate and how to attempt removal. As with any device, the instructions for use are periodically updated. And recently more guidance on how removals should be performed was added based on published literature and case studies. Prospective clinical trials of removal techniques have not been done. Ultimately, it's the clinical judgment and surgical expertise that must be used by the -- must be used to guide physicians as the best approach for each unique or different patient situation.

This table is showing the data for removals for the Phase II, pivotal, which was up to 5-year follow-up, and the most recent TVU study. Removals were done via a number of techniques: laparoscopic salpingectomy, cornual resection, and hysterectomy. Most of the hysterectomies, however, were not related to Essure itself but done for other reasons such as bleeding or pain from other gynecologic pathologies or sources.

Most published literature on removal focuses on individual case reports, which correct the misperception that hysterectomy is the only effective way to remove Essure. The case reports show that the inserts can be successfully removed via hysteroscope if the removal is attempted up to 7 weeks post-placement. Cases also report successful removals via linear salpingostomy or salpingectomy either through the laparoscope or laparotomy. Laparoscopic salpingectomy has been described from 10 weeks up to 4 years post-

placement. Now, cornual resection can also be used to perform -- can also be performed, but the patient should be counseled about an increased risk of hysterectomy with this particular procedure. It's also important that the location of the insert is confirmed prior to any removal procedure in order to minimize the need for future surgical interventions.

From our postmarketing monitoring database, the principal reason for removal is unsatisfactory location. Bleeding disturbances and pain are also cited. And the reporting frequency is 0.11%.

So, in conclusion, data from clinical studies, literature, and postmarketing monitoring show that the need for Essure removal is infrequent. The method of removal will be different for each patient and will depend on the location of the insert, her symptoms, as well as any other pathologies such as fibroids, endometriosis, or adenomyosis.

Now, while the literature is somewhat limited on removal techniques and methods, it is clear that removals can be successfully accomplished without the need for hysterectomy in the majority of cases.

The specific technique and the instruments to be used must be guided by general gynecologic and surgical principles that gynecologists are expected to have. It is important that the physician involve the patient in the decision on what specific technique and what method is best for her, given her symptoms and other possible gynecologic pathologies.

It is well accepted that all medical procedures carry the risk of serious adverse events, including death. It is devastating for the family and devastating for the physician when this occurs. And we have a few deaths associated with the use of Essure through

reports since 1998.

Here is what is known about death in association with Essure. From the clinical trials, two deaths were reported. Both were unrelated to Essure. One was due to leukemia, and the other was due to a myocardial infarction post-bypass surgery. In the literature there are no reports associated of death with Essure placement.

In the postmarketing monitoring there are seven cases of death; however, none were directly caused by the inserts. There were three anesthetic complications, which included a case of a suspected air embolism during the placement procedure. There was one case each of cardiac arrest, sleep apnea, Group A strep, and a pulmonary embolism that occurred during a hysterectomy.

So, in conclusion, deaths specifically due to the inserts have not been reported, and the risk associated with the Essure procedure is low and is in line with laparoscopic tubal ligation fatality risks.

Pregnancy outcomes is the final topic of interest we will address this morning. Essure is effective and only a small number of pregnancies occur in these patients. There were four luteal phase pregnancies in the pivotal study, and this means that these pregnancies occurred or had begun before the Essure procedure was done. None of the pregnancies were continued. One woman who had a successful bilateral placement later decided to undergo in vitro fertilization with the Essure inserts in situ. The result was a healthy baby. There were also four pregnancies in the recent transvaginal ultrasound study. Two were terminated, and two had an early miscarriage.

There is limited reporting in the literature on the outcomes of unintended

pregnancies. Postmarketing analysis of the available data and information on pregnancy outcome reports that the reporting frequency of pre-term events, such as stillbirth and fetal anomalies, are within the expected ranges for women of the same average age group as Essure users.

But it may be more informative to look at outcomes of desired pregnancies with Essure in place, when it is used off label for the treatment of hydrosalpinx in a woman prior to an in vitro fertilization procedure. Because these are desired pregnancies, they are closely followed, and the outcomes are well documented.

We examined the published systematic review that identified 11 studies of 115 women using Essure before IVF for hydrosalpinx. There were 54 pregnancies. The pregnancy rate was 39% per embryo transfer. The live birth rate per embryo transfer was 29%. In a separate study, comparisons to salpingectomies in the same setting have shown comparable pregnancy rates and outcomes.

So, in conclusion, the data suggests no evidence that Essure increases the risk of adverse fetal outcomes.

So Essure research spans over a decade. We have data on over 10,000 women. That data affirms that the safety and efficacy of Essure is consistent across all data points, clinical trials, independent literature, and postmarketing surveillance. In addition, ongoing studies continue to follow over 3,000 women.

So, now to continue our presentation, Dr. Cindy Basinski will be speaking today about her and her patients' real-world experiences with Essure.

Dr. Basinski.

DR. BASINSKI: Madam Chair and Advisory Committee members, I would like to thank you for giving me the opportunity to speak today about my and my patients' real-world experiences with Essure.

For background information, I graduated from Purdue University with a biomedical engineering degree and obtained my medical degree from Indiana University. I completed a general surgery internship and completed an OB/GYN residency with a focus in urogynecology under the guidance of Drs. Tom Benson and Doug Hale. I am board certified in female pelvic medicine and reconstructive surgery. I have published articles in the fields of general surgery, urogynecology, and in-office gynecologic procedures.

I wish to disclose that I have been involved with consulting work for Bayer, in education and training of physicians, with a focus in the area of patient counseling. I have been compensated for my time and travel for this meeting, but I have no financial interest in Bayer.

A little bit about myself. I am a private practice physician practicing in a small community in Indiana since 1999. My community is built around manufacturers such as Toyota, Alcoa, GE, and Bristol-Myers, by whom many of my patients are employed and insured. I spend half of my time practicing urogynecology, caring for conditions such as incontinence and prolapse, and the other half of my time in minimally invasive gynecologic surgery, with a focus on in-office gynecologic services. I have been performing in-office procedures since 2006, including operative hysteroscopy, cystoscopy, endometrial ablation, and Essure. In the past 9 years, I have performed over 1100 Essure procedures. In 2006 there were very few physicians performing in-office procedural -- offering in-office

procedural options. With my gaining experience, it was the first time -- it was at that time that I was asked to share my personal knowledge about patient counseling, safe in-office pain control protocols, and procedural setup with other physicians, allied health personnel such as nurses and administrators, as well as residents and students.

In 2009 I was involved with the American Medical Association and the Centers for Medicare and Medicaid with coding and payment for in-office gynecologic procedures, as I believe these are important avenues for care of patients.

Since that time I have become deeply interested in clinical research. I have been involved in several pre- and postmarket FDA trials for in-office technologies. I am also an advocate for physicians creating personal databases with patient outcomes for the various procedures and treatments they provide. I also try to find time to report data in the literature to share personal experiences and patient outcomes when the data seems relevant.

In 2013, when I began hearing more concerns with Essure, I wanted to create a database of my first 1,024 patients and review outcomes with these patients. Some of the interesting data that was found in that review was that we had 1,732 women-years of follow-up, with an average follow-up of 1.7 years in a range of 0 to 8 years. We found a 94.4% intent-to-treat reliance right in our population. Nine patients experienced perforation, which represented 1.2% of my population, and that rate is consistent with the 1.8% rate seen in the clinical trials. We also noted that patients with a perforation -- no patient with a perforation requested removal or reported pain. There were six expulsions, which represented a 0.8% rate, which is also consistent with the clinical trial rate of 2.2%. I

had one patient request device removal due to pain. Her devices were removed at 3 weeks after placement with a laparoscopic procedure, and her pain resolved. No reports were documented of any allergic reactions or autoimmune symptoms in this population. We had two luteal phase pregnancies despite negative pregnancy test at the time of their procedures. Both patients resolved their pregnancies and went on to rely on Essure for the contraception.

Based on the data review in my practice, Essure outcomes were consistent with the data that was seen in the clinical trials and provided a good contraceptive option for my patients.

We need contraceptive options for our patients. Based on data from the CDC National Survey of Family Growth in 2010, 36% of women who did not want any more children were using temporary methods to prevent pregnancy, and astonishingly, 8% were using nothing at all. I was made acutely aware of this issue once I began offering Essure to my patients as an option.

I thought I was actually doing a pretty darn good job of talking to my patients about contraceptive care, and once I started talking to them, I realized many of them were not using anything, and I began to ask them why they weren't using anything. A lot of them said that they did not want to use hormonal products because those products cause them headaches, decreased sex drive, weight gain, and other reasons. And some women couldn't use hormonal medications because they had health problems that prohibited them from doing so. They knew tubal ligation was an option; they just didn't want it. They didn't want to have surgery; they didn't want to miss time away from their families. And so there was

no good option for them at that time.

So I began to talk to them about the Essure procedure, and many of my patients were very interested in this option. The idea that they could have a procedure in the office without anesthesia, incisions, or hormones and return to work the next day was ideal for a lot of my patients.

Since I've been performing Essure procedures for over 9 years with high patient success, I'm often asked what I feel contributes to optimal patient outcomes. When it comes to real-world use of the Essure devices, three components are essential for optimal patient outcomes. First is that physicians must be skilled to perform hysteroscopic procedures. Second, physicians must be knowledgeable about available data concerning Essure and its proper usage. Finally, physicians must be able to translate that knowledge to their patients to properly educate them about the Essure product.

But the most important overriding issue for optimal patient outcome is choice. And, in the case of permanent contraception, there are only two choices available right now. It is important to remember that while both laparoscopic and hysteroscopic procedures are considered overall safe and effective, there are very large differences between these approaches for permanent contraception that are meaningful to women.

Laparoscopy inherently involves specific risks that are often avoided with a hysteroscopic approach. When approaching a tubal ligation laparoscopically, incisions are required to be made in the abdominal wall, instruments inserted into the abdominal cavity, directly exposing internal abdominal content such as bowel, blood vessels, liver, and spleen to surgical instruments 100% of the time. In addition, all tubal ligation procedures

necessarily involve the destruction of the fallopian tubes, often with electrical energy sources that cannot only heat the fallopian tubes, but risk transfer of energy to surrounding organs. If electrical energy is not used, suture, metal clamps, or silastic bands can be used to clamp the tube, leaving foreign material in the abdomen. Furthermore, a laparoscopic procedure necessarily requires general anesthesia and an operating room.

A hysteroscopic approach uses the natural pathway of the vagina and cervix to enter into the uterine cavity, seldomly exposing instruments to the internal abdominal cavity. No energy is used when inserting the Essure devices, and no destruction of the fallopian tube is undertaken. An advantage of hysteroscopy is that it can be performed in a physician's office with no general anesthesia.

It is important to recognize that all tubal ligation procedures result in scarring of the fallopian tubes to create blockage and prevent pregnancy, whether it is laparoscopic or hysteroscopic. And foreign material such as suture, metal, or silicone can be left in the body even with laparoscopic procedures or other surgical procedures in medicine.

But we must keep in mind that optimal patient outcomes with either laparoscopic or hysteroscopic permanent contraception is premised on the underlying skills of the physician, and the value of good hysteroscopic skills is an important aspect of the Essure procedure.

Overall, hysteroscopic abilities are related to (1) basic hysteroscopic skills acquired in residency or other physician-to-physician training program; (2) how often operative hysteroscopic techniques are applied on a day-to-day basis in a physician's practice is significant, as we know that the more a physician uses a skill, the more likely they are to be

good at that skill and less likely they are to have complications; and if the physician seeks additional training to improve or increase operative skills.

In an effort to increase and improve operative hysteroscopic skills for physicians, many avenues of education have been created since the introduction of the Essure device in 2002. Tremendous effort has been focused on making Essure an integral part of residency education and procedural training for residents. In addition, if one partner of a group of physicians demonstrates sufficient hysteroscopic skills, often that physician will take the lead in helping his or her partners in better performing the hysteroscopic procedures.

Governing organizations within OB/GYN, like ACOG, AAGL, or SLS, have advanced hysteroscopic skills by offering workshops with hands-on training with known expert hysteroscopists. However, multiple private industry organizations have also partnered with each other and with governing organizations, like ACOG, to create additional learning opportunities.

Seminars have been offered by Conceptus, and now Bayer, in conjunction with hysteroscopy companies to provide educational programs. These programs offer physicians, who desire to learn more about hysteroscopy and the Essure procedure, the chance to work one-on-one with a very experienced hysteroscopic physician. Once a physician feels they have good hysteroscopic skills, they may choose to enter into the Bayer Clinical Pathway to perform the Essure procedure.

However, once a physician has gone through the Clinical Pathway, the opportunity for further education is provided. Peer-to-peer opportunities are available to physicians who seek additional proctor or consultative information. And I'm involved in the Bayer

consultancy network, and this is a new program that was developed over the past 6 months. Any physician who has a question in the United States regarding the Essure product can place a request to speak with a consultant like me. Once I receive the request, I will make contact with the physician within 24 hours. Some of the situations I may assist physicians to solve is offering advice on device removal or interpretation of HSG results or management of patients with complications.

The proctoring program offers physicians the opportunity to have a physician present for a procedure to receive hysteroscopic or Essure-related training to improve technique or patient outcomes. I personally have been involved with proctoring programs in which physicians, nurses, and office managers have actually come to my practice to learn about appropriate safety and relevant procedural-related issues to have a safe Essure procedure in the office.

I also use the proctoring program as an opportunity to educate physicians about patient counseling, for which I have a very strong belief is one of the most important aspects of patient care. I absolutely believe that physicians should not be telling patients what they need to do, but rather giving them accurate and up-to-date information about options available to them.

Once patients have good information, they can decide what is right for them. Contraception is a quality-of-life issue that is about choice. Whenever it comes to contraception, we should understand whether patients desire reversible options for which birth control pills, IUDs, injectables, or implantables may be most appropriate, or if they're interested in permanent options, for only which two options are available. That's

abdominal or laparoscopic approach or hysteroscopic approach.

If a patient chooses a hysteroscopic approach, it is very important, as a physician, that I provide them with reliable and accurate data. Many types of clinical information are available to physicians and patients that include prospective, retrospective, case report, and anecdotal evidence. It is important to be aware of all of these types of information, but clearly we know that scientific collection of information is important, and that when women make decisions, physicians need to present good scientific information to our patients.

In the case of Essure, there is this very good scientific data about the high efficacy and positive safety range of the procedure. The use of the FDA pre- and postmarket clinical trial data has been reviewed by experts in the FDA, stringently monitored by national organizations and risks properly adjudicated, and is the most important source of counseling that I use to help patients understand risks and benefits of the Essure procedure. However, there are hundreds of additional publications in the literature with over 10,000 patients in support of the FDA clinical trial experience.

The likelihood of a successful bilateral placement is 97%. But patients should be made aware that there is a 3% chance their procedure will not be completed. The need for confirmation testing is an important aspect of the procedure, and a patient must understand and agree to this. Risk and complications such as device perforation, expulsion, or patient patency should be explained. In fact, this is a time where I can reinforce the need of the confirmation test to make sure that they know this is the only time we can identify those types of events.

If a woman is using a hormonal medication to suppress pelvic pain or heavy

bleeding, women should be aware that cessation of these medications after any sterilization procedure may result in a recurrence or exacerbation of pain or bleeding once they stop their medication. Each patient has a very unique medical history, and physicians must be cognizant of factors that may make one approach suitable over another.

I also like to make sure that patients have an opportunity to actually touch an Essure device. I want them to put it in their hand, I want them to feel it, I want them to understand what's going into their body, and I want them to ask me questions. And I also talk to them about the other places that devices like this are used in the cardiac field and the orthopedic field and dental field so that they can ask questions about that, too.

True informed consent is a very active process for both physician and patients. I try to explain procedures using multiple modalities. I want to speak to you in words that you understand and make sure that you're hearing what I'm saying to you. I also want to make sure that I give you written information that's available so that you can understand the procedures that you're having. And I also draw pictures. I want you to see on a picture where an Essure device sits and what a perforation may look like if that would happen. And, finally, I want my patients to know that if a complication should happen, how I am going to help you take care of that.

While gynecologists understand the great difference in benefits and risks with laparoscopic and hysteroscopic approaches to permanent sterilization, the need for continued responsibility of industry, oversight agencies such as the FDA, and organized medicine to continually obtain data is recognized to be important by all of us in the healthcare community. Physicians should be vigilant to look for good and bad outcomes in

their patients. However, we still have to rely on good scientific data and information to counsel our patients and guide their decisions.

I certainly appreciate that not all women can have a good outcome with Essure, as is the case with any surgery or procedure. Proper and conscientious discussion of benefits and risks must be performed. However, for the over 1,000 patients in my practice relying on Essure, Essure has proven to be a valuable and desired contraceptive option.

Thank you.

DR. CARNEY: Madam Chair, members of the Committee, and guests, thank you for this opportunity to speak. My name is Dr. Patricia Carney, and I'm the Director of U.S. Medical Affairs, Women's Health, with Bayer HealthCare.

Prior to joining Bayer, I spent 17 years as a private practitioner and then as an academic physician. For several years I served as a residency program director, educating our future OB/GYN residents. And I had the honor of serving as an oral board examiner for the American Board of Obstetrics and Gynecology. One of my most important jobs as a physician, however, was patient counseling. Every procedure, device, drug, and decision in medicine carries both benefits and risks. Helping put this information in the proper context for patients is a vital part of the informed consent process.

When I was in practice and I needed to counsel a patient about a risk of a particular procedure, I would, of course, say the risk of something is one in however many. What I always told her, however, is that if she was the one, the risk was 100%. We know that an adverse outcome for an individual patient can be devastating, and this should never be minimized. Still, when looking at benefit-risk, we do need to understand the profile for all

women.

According to the ACOG practice bulletin on benefits and risks of sterilization, counseling should be comprehensive and include a discussion of technique, efficacy, safety, potential complications, and the alternatives to female sterilization. Benefit-risk must take into account not only the specific procedure under discussion, but also all alternative options to that procedure.

It is important to make sure patients understand the limitations of different data sources. Only after an appropriate discussion of benefit-risk, in context with alternative procedures, as well as the baseline risk for specific outcomes in the general population, can a patient make a truly informed decision. In addition to this overall analysis, the discussion should also include how particular risks can be mitigated should they occur.

Women should be counseled to utilize the most effective method of contraception they're willing to use. For women who are sure that they have completed their childbearing, this includes permanent birth control options. The decision not to use any contraception at all also carries risk, since pregnancy itself can be accompanied by serious and sometimes fatal outcomes. In addition, no method of contraception is 100% effective, and this includes permanent birth control methods.

Once a patient decides she's interested in a permanent birth control option, the specific procedure needs to be selected. There are many factors that may influence her choice. For Essure, the instructions for use outlines the requirements for this counseling process, part of which is shown here on the slide. As pointed out, the decision to undergo treatment is at patient discretion following physician counseling and informed consent.

Essure has a number of benefits. As Dr. Zampaglione described, both clinical trials and independently performed studies demonstrate high efficacy when Essure is placed properly and there is a satisfactory confirmation test. The procedure does not require general anesthesia. It can be performed in the office setting and does not require entry into the peritoneal cavity.

Patients also need to be aware that due to variations in anatomy or other issues such as difficulty with visualization of the tubal ostia, Essure may not be successfully placed in a small percentage of cases. Data from the clinical trials indicate that this occurs in approximately 3% to 4% of cases.

The Essure inserts contain nickel with a potential for allergic reaction. This information has always been in the instructions for use.

It is crucial that patients are made aware that compliance with 3 months of alternate contraception and the Essure confirmation test are essential for success of the procedure.

Patients also need to be aware that after the confirmation test, a small number of women, approximately 3%, will be told that Essure is not in the proper location and that they will not be able to rely on it for contraception. A plan needs to be in place as to what is the next step in assuring effective contraception for this woman.

Specific adverse events such as pain, perforation or other unsatisfactory location, menstrual changes may occur in a small number of women.

While highly effective, no method of contraception is 100%, and pregnancies have occurred in women with Essure.

As an alternative to Essure, laparoscopic tubal ligation is a safe and effective method

of permanent birth control.

While there are no head-to-head prospective clinical trials of Essure versus tubal ligation, extensive data exists for both procedures, including some comparative studies.

Once a bilateral tubal ligation is performed, the method is immediately effective, and there's no need for additional patient compliance. Occasionally, however, it is not technically possible to actually complete the surgical procedure, and an alternative method of contraception then needs to be used in this patient.

Laparoscopic tubal ligation, however, is not without risks, some of which can be very serious. Risks of laparoscopic tubal ligation include bowel injury, particularly at the time of Veress needle or trocar insertion. A recent systematic review by Llarena et al. in 2015 estimated that the risk of bowel injury specific to laparoscopic tubal ligation is 1 in 3,333 cases. Injury to the major blood vessels of the pelvis is rare but a potentially fatal event, with an estimated risk of approximately 1 in every 5,000 laparoscopic procedures.

While tubal ligation is very effective, the overall 5-year risk of pregnancy is 13 per 1,000, or 1.3%, when all types of laparoscopic sterilization methods are considered. Should pregnancy occur, the risk of ectopic pregnancy may be as high as 65% with some methods of tubal ligation, such as bipolar cautery. In addition, the procedure requires the use of general anesthesia, and complications with general anesthesia can occur.

Laparoscopic tubal ligation can be performed in a variety of ways. The Filshie Clip and Falope-Ring are two commonly used devices. The instructions for use for the Filshie Clip includes the information shown on the slide. As you can see, placement of these devices laparoscopically can result in pelvic pain, musculoskeletal pain, clip migration or

expulsion, and misapplication of the device.

Similar AEs are seen with Essure. In this table we see adverse events from the day of the placement procedure.

This table reflects the adverse events experienced by women during the first year of reliance, based on the pivotal trial.

Both of these tables are presented in the instructions for use for Essure.

In conclusion, all permanent birth control procedures carry risk. It is important to balance these risks with the benefits of the option under discussion, in addition to the risks and benefits of alternate procedures.

The efficacy and safety profile of Essure is well characterized and compares favorably to the benefit-risk profile of bilateral tubal ligation.

We at Bayer continue to work to mitigate the risks associated with Essure. This includes information in the instructions for use and the patient information booklet, educational materials such as patient and physician websites, well-constructed and updated physician training, patient counseling materials, and programs to support the needs of physicians and their patients.

Women deserve safe and effective options when it comes to permanent birth control. For the properly counseled patient, for the patient who meets the criteria outlined in the instructions for use, Essure is a good option. Hundreds of thousands of women have benefited from the availability of Essure. Our assessment concludes that the overall benefit-risk profile of Essure remains positive.

Thank you.

DR. IGLESIA: Thank you very much. I'd like to thank Bayer HealthCare for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? Please remember that the Panel may also ask the Sponsor questions during our Panel deliberation session this afternoon.

Introduce yourself.

DR. ELSER: Denise Elser.

My question is, based on your rates of long-term follow-up as far as perforation or other complications, is there any demarcation between the different forms of the device after changes were made?

DR. ZAMPAGLIONE: No, the pivotal and the Phase II studies used the STOP, the initial coil, and then the ESS205 was studied and then the 305. And what was seen really from the transvaginal ultrasound, there really is not a significant difference in the safety and efficacy that was noted. Those changes were very minor to the coils.

DR. IGLESIA: I actually do have a question. In terms of intent to treat, I just notice on your 1-year follow-up on the pivotal trial, your *n* initially was 558, and the 1-year follow-up was 441, and I was just wondering what attempts were made for the retention and any kind of follow-up on the 110 patients or so that were lost.

And then my second question is what comparison studies do we have right now, head to head, on permanent sterilization options, laparoscopic abdominal versus hysteroscopic?

DR. ZAMPAGLIONE: Sure. Let me answer the second part first. We do not have any

head-to-head or direct head-to-head studies with bilateral tubal ligation with a laparoscopic or laparotomy. There were some comparative studies that were shown during the presentation, but not true prospective head-to-head studies.

For the first part of your question, I'd like to call up Dr. Kimberly Rosen. She's our clinical development lead for Essure and will be able to answer that question.

MS. CHAUHAN: Cynthia Chauhan.

DR. IGLESIA: Let them answer this one.

MS. CHAUHAN: Oh, I'm sorry, I thought he was finished.

DR. ROSEN: Good morning. Kimberly Rosen, Bayer HealthCare. Thank you for the question.

Just to clarify, in the initial pivotal study, there were initially 518 women enrolled in the intent-to-treat population; 507 of those women had device placement attempts, and a total of 464 women had bilateral placement, I believe, is the number. So we would only have followed women who had at least one insert in place after the placement procedure was accomplished. Regardless of whether or not women were instructed to rely on their inserts for birth control, they were followed for safety in that study if they had at least one insert in place.

DR. IGLESIA: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Thank you.

When you were talking about unsatisfactory location, the percentage differences in Spain and Canada were quite significant, I thought. Can you comment on that?

DR. ZAMPAGLIONE: It is hard to comment on that one because these are outside of the U.S. and, you know, the training programs are essentially the same. There are, of course, going to be some country differences. The materials, everything used are the same. But it is very challenging to start trying to compare different countries just due to different practice patterns. But the same device, the same system is used worldwide.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

I have one question. Of your perforations, what percentage of the devices fractured versus intact in these situations?

DR. ZAMPAGLIONE: So let me bring up Dr. Kimberly Rosen again from our clinical development. She's in the best position to answer that question.

DR. ROSEN: Thank you.

So, in the pivotal and the Phase II study, we do have one report of a device being fractured during attempted removal hysteroscopically. The device was placed and then attempted to be removed through the hysteroscope, and that device fractured. The only other reports of device fracturing that were -- that come from those two studies are during surgery either for hysterectomy or device -- or completion of a sterilization procedure in women with a perforated or unsatisfactorily located device, where the device was transected during the surgery. During the TVU study, which is currently ongoing, we do not have any reports of the insert breaking.

DR. IGLESIA: Okay, we will now take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members

inside or outside of the audience. We will resume at -- Shanika?

MS. CRAIG: 9:41.

DR. IGLESIA: 9:41. Thank you.

(Off the record at 9:32 a.m.)

(On the record at 9:50 a.m.)

DR. IGLESIA: Okay, if everyone can please be seated, we'd like to get started. At this time you will hear a presentation by the FDA.

I'll remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA, you may begin.

DR. CORRADO: Good morning, Panel members and guests. Thank you for participating in this public meeting to discuss the Essure system for permanent birth control that was approved by FDA in 2002. I'm Julia Corrado, a medical officer and clinical reviewer from the Office of Device Evaluation, which reviews medical device submissions prior to marketing.

We have just heard from Bayer HealthCare, the Sponsor of Essure, and later today we will hear the experience of members of the public. At this time you will be hearing three publications from the FDA. I will present some milestones in female sterilization, a snapshot of premarket review and PMA approval of Essure, and an overview of the current clinical landscape for female sterilization --

DR. IGLESIA: We need microphone assistance.

(Pause.)

DR. CORRADO: Dr. Ron Yustein, Deputy Director of the Center for Devices and Radiological Health's Office of Surveillance and Biometrics, our postmarket review office, will provide a comprehensive review of safety outcomes data on Essure. Next, Allison O'Neill will present the epidemiology review of effectiveness data on Essure. We hope the FDA presentations will provide clarity and transparency regarding the FDA review processes for Essure. Later today, FDA will be posing multiple questions for the Panel members to discuss. We're looking forward to hearing your discussion and recommendations based on what you have heard today.

As discussed in the background section of FDA's Executive Summary for this meeting, we believe the first publication on tubal ligation appeared in 1881. After this date and prior to 1930, multiple authors contributed to literature on this topic, but we think that it is appropriate to highlight the first report describing Ralph Pomeroy's technique of tying off with resorbable suture and resecting a loop of fallopian tube. That appeared in 1930.

The early to mid-20th century was a period of technical innovation in laparoscopic surgery. What may be the first published account of minimally invasive laparoscopic tubal sterilization appeared in a Swiss journal in 1936; however, the actual technique is unclear. A more recent but still earlier report describing electrosurgical laparoscopic sterilization using unipolar current appeared in a French language journal in 1962. Bipolar current was introduced in the 1970s to prevent thermal injuries with unipolar current. Also in the 1970s and early 1980s, occlusive tubal implants were introduced. The Essure system was the first of two hysteroscopic sterilization systems that made it possible to achieve incision-free

female sterilization and without general anesthesia. Essure was approved in 2002. The availability of hysteroscopic sterilization in 2002 also transitioned female sterilization from the operating room to an office setting.

In summary, tubal ligation was largely a laparotomy procedure from the late 1800s until the 1960s, when innovation in laparoscopic instrumentation led to adoption of minimally invasive, that is laparoscopic, sterilization. Female sterilization was still confined to the OR for another 30 to 40 years before further innovation led to office-based hysteroscopic sterilization after 2002.

This slide, the title of which is Sterilization Utilization in U.S., is intended to provide again a high-level overview of numbers of sterilization procedures. Female sterilization is among the most commonly performed surgeries in the U.S. Our estimate of annual incidence on this slide is based on several references using data from the 2002 National Survey of Family Growth and ranged from approximately 640,000 to 700,000 annual procedures.

FDA does not regulate sterilization; however, FDA does have regulatory authority over medical devices used to perform these procedures. As I will discuss on the next slide, this authority is most relevant as it relates to devices used in radiofrequency electrosurgical sterilization, laparoscopic occlusive devices such as Hulka clips, Filshie Clips and bands, and Essure.

Regarding postpartum sterilizations that comprise about half of the 600,000 to 700,000 annual sterilizations, surgeons typically use manual surgical instruments such as scalpels, which are Class I devices. These instruments are not specifically indicated for

female sterilization; therefore, FDA does not regulate them for such intended uses. Manufacturers of these devices are required to register with FDA and declare their products conform to general controls, including manufacturing quality and labeling.

In contrast, FDA does review premarket submissions for Class II laparoscopic instruments and electrosurgical accessories under Class II. These devices require premarket notification through the 510(k) pathway in order for FDA to determine whether they are substantially equivalent to other legally marketed devices.

Class III devices such as laparoscopically placed clips and bands that are specifically indicated for tubal sterilization and hysteroscopic tubal occlusion systems require premarket approval through the PMA process. This means that sponsors of these devices cannot claim substantial equivalence to another device. Rather, the sponsors must provide reasonable assurance that the device is safe and effective for its intended use. The level of evidence to support PMA typically includes a pivotal clinical trial.

In the next several slides, I'm going to provide just a snapshot of the evidence for FDA's approval of the Essure PMA in 2002.

Both the Phase II and pivotal clinical trials were prospective, multi-center, international single-arm studies. The landmark CREST study provided a historical control against which to compare the effectiveness of Essure against multiple methods of surgical tubal ligation. The Essure pivotal trial enrolled subjects in such a way as to age-match Essure and CREST participants. Follow-up to at least 5 years following sterilization procedure was available for both the Essure and CREST studies.

Availability of CREST outcomes data led FDA to conclude that a concurrent control of

surgical tubal ligation was unnecessary to obtain "reasonable assurance of safety and effectiveness" of Essure as required under Section 513(a) of the Federal Food, Drug and Cosmetics Act. And I would note that a representative from the CDC made a presentation on the CREST study to the FDA Advisory Panel in 2002.

Outcomes from the Phase II and pivotal trials were pooled to provide contraceptive effectiveness data on 632 women at 1 year and 197 women at 2 years when the Sponsor and FDA presented the PMA to the Advisory Panel in 2002. A slightly higher number of subjects contributed to the safety outcomes review. This group included women, as we've heard earlier today, who had received at least one Essure insert but who were not relying on Essure for pregnancy prevention.

This slide is a summary of the safety data presented to the 2002 Advisory Panel. Additional data was also provided, but this slide does appear in the summary of safety and effectiveness for Essure. It can also be found in the appendix to the Executive Summary for today's meeting.

Included in this table are pain, headache, and change in bleeding. That will be discussed in detail along with other adverse events in Dr. Yustein's presentation. I'd like to add that at the time of the Essure Panel meeting in 2002, data on device perforation and expulsions that prevented reliance on Essure were also discussed.

As the Sponsor has already discussed, Essure is a sterilization method. Unlike tubal ligation, Essure is not a one-time procedure. There are three mandatory steps that must be completed before a patient may rely on Essure. These are insert placement, use of alternate contraception, and presenting for the Essure confirmation test. FDA's analysis of

Essure's effectiveness is based on the clinical trial participants who completed the three-step method. The prospective IDE study protocol for the pivotal trial specified that any pregnancy that occurred prior to completing all three steps would not be counted as Essure method failures. All product labeling, including patient labeling, is explicit regarding adherence to the three-step procedure.

This slide presents the number of participants in the Phase II and pivotal trials combined. Please note that the first number in these boxes refers to the Phase II study, and the second refers to the pivotal study. As you can see, 227 participants from the Phase II and 518 from the pivotal study underwent attempted bilateral insert placement. There were 81 participants who did not -- who were placement failures; 664 had successful bilateral placement. Of these, 643 underwent the confirmation test and were advised to rely on Essure; and of the 643, there were 1-year follow-up outcomes data on 632.

Reasons for the inability to rely on Essure included perforation, expulsion, and tubal patency. Table 4 in the Executive Summary provides numbers of study subjects who at least initially could not rely for the above reasons, although some subsequently may have been able to rely.

This slide provides the pregnancy outcomes, in the pink boxes off to the right, for the combined Phase II and pivotal trials. As the Sponsor noted, there were four pregnancies determined to have been conceived prior to the insert placement procedure based on early first trimester sonogram. There were no pregnancies at the 1-year anniversary of reliance on Essure. Two-year outcomes data at the time of the 2002 Panel meeting were available for 197 participants. There were no pregnancies among the subset of trial participants.

Based on the safety and effectiveness outcomes from the Phase II and pivotal trials, the result of the 2002 Panel meeting was as follows:

- The Panel found a favorable benefit-risk profile for Essure;
- They voted to recommend approval by a vote of eight recommending approval, zero recommending disapproval, and one abstention;
- Conditions of the approval, however, included continuation of the clinical trials out to 5-year follow-up following reliance on the device and a new study to evaluate placement rates in newly trained physicians.

In my last two slides I'm going to turn to the topic of the broader clinical landscape in which a patient considering permanent sterilization might find herself. To start with this slide, I'd like to present a high-level comparison of hysteroscopic sterilization with tubal ligation. Regarding adverse events, Dr. Yustein will be providing detailed outcomes data on Essure's safety after my presentation.

We presented the summary of safety outcomes following tubal sterilization in the Executive Summary, and we relied for that on an analysis by Jamieson et al. of approximately 9,500 participants in the CREST study. Six categories of outcomes were evaluated by Jamieson et al.

1. Unintended major surgery
2. Transfusion
3. Febrile morbidity
4. Life-threatening event
5. Rehospitalization

6. Death

No deaths were reported in this group.

The rate of women who experienced any of the above events -- and again, we're talking about tubal sterilization -- was 153 out of 9,475, or 1.6%. Independent predictors of any complication were diabetes mellitus, general anesthesia, prior abdominal or pelvic surgery, and obesity.

Regarding the other outcomes in this list, the comparative pregnancy risk at 1 and 5 years, as presented in the Essure patient brochure, is listed here, and FDA reviewed those numbers. The timing of effectiveness is a minimum of 3 months for Essure compared to immediate effectiveness of tubal ligation, again, the point being that these numbers reflect women who successfully completed the method, the three-step method, and were told to rely. The need for patient compliance is high for Essure relative to tubal ligation.

Regarding the actual procedure, Essure requires neither a skin incision nor general anesthesia and can be performed in the office as opposed to the operating room. Interval tubal ligation does require a skin incision and is performed under general anesthesia in the OR.

Here I'm departing somewhat from the narrow discussion of sterilization to include a comparison of Essure and long-acting reversible contraception, or LARC. As you know, LARC includes both non-hormonal (for example, the ParaGard copper IUD) and hormone released in products (for example, levonorgestrel-releasing intrauterine systems as well as etonogestrel-releasing subdermal implant). All are indicated for prevention of pregnancy, and one has an additional indication for treatment of heavy menstrual bleeding for women

who choose to use intrauterine contraception as their method of contraception. These LARCs provide pregnancy protection for 3 to 10 years.

The reason for including this slide is to acknowledge one of the findings from the CREST study, which was that cumulative risk of sterilization regret within 14 years following sterilization was 20% for women 30 years or younger versus 6% for women who were older than 30 at the time of sterilization. Women who are even slightly uncertain about their desire for sterilization may be offered LARC products. As with Essure, there are risks associated with LARC products, which are described in detail in approved labeling, that is, the prescribing information for these products.

The most commonly reported adverse events in the clinical trials of all four of the hormone-releasing products are acne, headache/migraine, abdominal discomfort or pain, and breast tenderness or pain. Abnormal bleeding is listed under the most commonly reported adverse events category for three of the four hormone-releasing LARC products.

Device expulsion or migration is listed as an adverse event in the labeling for all LARC products; however, this event is not listed among the most commonly reported adverse events for those products.

As you can see, pregnancy risk is similarly low for hysteroscopic and LARC methods. There are important contrasts between these types of contraception regarding the timing of effectiveness, the need for patient compliance, and the need for a skin incision.

To conclude, for women contemplating permanent birth control, the clinical landscape is complex. FDA attempts to address this complexity by providing detailed safety information in physician and patient labeling. It is impossible, however, to include every

single type of adverse event reported in clinical trials and device labeling.

As part of our total product lifecycle approach to medical device review, we are constantly reviewing new safety and effectiveness information and require revised labeling when it is warranted. For PMA products, we can require the sponsor to have FDA review every change they make to labeling, and FDA frequently proactively requests such changes.

We are looking forward to your deliberations this afternoon. I'll turn the podium over to Ron Yustein, who will discuss both premarket and postmarket safety outcomes data for Essure. And thank you for your attention.

DR. YUSTEIN: Good morning. Again, my name is Ron Yustein, and I will be presenting our safety review for the Essure device, and then Ms. O'Neill will present effectiveness results after that.

Before starting, I wanted to describe the sources of information considered in our review, which are shown here, as well as the topics we focused on. One source of data was the 5-year follow-up of the cohort from the PMA Phase II and pivotal studies, which Dr. Corrado just described. The follow-up was ordered as a condition of approval and both conducted as post-approval studies. Both were completed by the end of 2007.

This table provides the number and percentage of patients providing data at each follow-up in those studies, with the percentage based on the number of subjects who had received at least one implant. Both studies had slightly over 80% of subjects available at the 5-year follow-up.

In slides I will show related to these studies, for events of pain and bleeding, a rate at a given follow-up represents the percentage of patients who experienced that event

since the previous follow-up. As these do not provide information related to persistent symptoms, the Sponsor, for the pivotal cohort, also provided recurrent rates, which represent the percentage of subjects reporting the event at more than one visit, and persistent rates, which represent the percentage of subjects reporting the event at all visits through that follow-up.

The ESS305, Study 16974, which I will refer to as the transvaginal ultrasound or TVU study, is a prospective, single-arm, multi-center study being conducted under IDE regulations. The Sponsor designed this to support approval for a change to the confirmation protocol. The study is ongoing, and the most recent annual report includes 2- and up to 3-year data on subjects. In their report, the Sponsor cited rates of events based on the 597 women who underwent Essure placement procedures. However, as of the last annual report, 493 subjects remain enrolled and are being followed. I will provide results for this study alongside Phase II and pivotal study results, as they were all three IDE studies.

A review of the literature was performed through June 2015 using the search criteria noted on the slide. In addition, case reports and abstracts were also reviewed for the specified adverse outcomes discussed today. There were significant limitations to the literature, and these will be discussed during our presentation.

The Sponsor already described their SUCCES II study. Although this is a large prospective study, it is being conducted entirely outside the United States and is not under IDE. In addition, it is worth noting, as the Sponsor noted, that although interim data are available on over 2,200 patients at 3 months and 1,200 patients at 2 years, beyond the 3-month visit, the follow-up questionnaire did not include any systematic data collection for

safety endpoints. Rather, unsolicited adverse events were captured in a free field section of the case report form.

We also reviewed the medical device reports submitted to FDA through May 2015. Although MDRs are a valuable source of information to monitor a device's performance under real-world use conditions, they represent a passive surveillance system and, as such, have important limitations. Numbers can be difficult to interpret as events may be underreported, or their numbers can be impacted by a change in the number of uses of the device, a recent regulatory action, or public attention. Unfortunately, MDRs often lack critical or complete information related to the patient, event, or outcomes. They cannot be used to calculate rates of events and often cannot be used to prove the device caused or worsened an event.

This graph depicts the number of Essure MDRs by year. A spike began in late 2013, and the majority of those were voluntary, seen in green, not manufacturer reports. It is important to note that the year listed is that in which the report was received, not the year of the event. Many reports submitted since late 2013 describe events that occurred in earlier years.

FDA also has received information related to the device from other sources, including communications with patient groups, pilot evaluations of social media sites, inspections of manufacturing sites, and information from global regulatory partners. Some of these are included in more detail in our memo but, because of the amount of data to present, will not specifically be presented this morning.

I also wanted to introduce the specific safety topics that are included in our review.

Taking a step back, this table was produced based on events listed by Essure patients on websites or in MDRs. We are not suggesting causality with the device in each of these. We are simply presenting the types of events publicly cited or within MDR reports.

FDA primarily reviewed events which were most commonly discussed, which appear to have significant impact on a patient's well-being and for which scientific data was likely available. This is not to downplay any of the other events reported, but we recognized a need to focus our review on a subset of those issues noted on the previous slide.

We tailored our safety review to chronic or persistent abdominal pain or cramping, bleeding irregularities, headache, metal allergy, perforation, migration, and device removal. Pregnancy issues will be discussed by Ms. O'Neill a little later. Many of these events are known complications and are already included in Essure labeling. Due to time constraints this morning and the amount of information to be provided, our presentation will provide overviews, and we refer you to our memo for more details.

All right. I will start off with post-procedural abdominal and pelvic pain or cramps. Although procedural pain is a well-known event, it typically resolves within hours or days. However, reports suggest that some patients experience more persistent pain events. One difficulty in assessing abdominal pain is the fact that it is a common symptom and, although may be due to the device, may also be the result of unrelated processes involving the digestive, genitourinary, reproductive, musculoskeletal, and/or nervous systems.

This slide presents data from the IDE studies. The results from the time of PMA approval are on top. The bottom represents data from their 5-year follow-up as well as the ongoing TVU study. The percentage of patients noting pain at the latest follow-up generally

ranges from 1% to 5%, consistent with the data at the time of approval. However, for the Phase II and pivotal studies, these are rates at the 5-year visit and only capture events occurring since that previous visit. They do not speak to rates at prior visits or the chronicity of symptoms for a given subject.

The graphs on the next several slides depict the rates of pain events in the pivotal cohort at each follow-up. This first graph represents general pelvic pain, suggesting rates of 3% to 6% at each visit during the first 18 months and lower subsequently. For dysmenorrhea, rates at each follow-up point also generally remained in the 3% to 5% range after the initial 3 months, and for dyspareunia, again, generally less than 3% to 4% at each visit following the 3-month follow-up.

The Sponsor presented this data which shows that, per their definitions, approximately 4% to 6% of pivotal trial subjects experienced recurrent pain during follow-up, and only one subject reported persistent pelvic pain, which lasted through 2 years. Again, the percentage of subjects providing data at each visit should be taken into account when evaluating the rates for pain, as persistent pain may have been a reason for patients exiting from the study with time.

Next, turning to the literature. Post-procedural chronic or persistent pain has not been a common outcome reported in the literature, and this slide captures the publications from our memo. Since they are described more there, I wanted to just make a few points.

The Sponsor noted the Conover paper in their presentation. However, the rates, although low, may be difficult to interpret. In addition to potential issues related to coding, women with only on pelvic pain diagnosis or women who had prescribed non-opioids or no

medications for their pain would not have been captured. On the other hand, the study assumes that opioids were for pelvic pain, and some women may have been included incorrectly. Furthermore, the hysteroscopic group included patients who had undergone the Adiana procedure as well as the Essure procedure.

The Yunker publication, which was a retrospective review, noted a 4.2% rate for chronic pain, which was defined as pain persisting for more than 3 months after insertion. The authors also identified preexisting chronic pain conditions as a risk factor for chronic abdominal or pelvic pain after Essure. This is particularly notable because the IDE studies, which we already discussed, and possibly others excluded such patients.

The two large cohort studies by Arjona-Berral and Povedano cite low rates of persistent pain; however, both represent retrospective reviews from the same institution. In addition, Arjona-Berral reported on patients who did not respond to standard analgesics and who underwent device removal. We do not know how many others in their cohort had persistent pain that did respond to analgesics and/or did not undergo device removal.

Sakinci cited a zero rate at a mean of 83 months. But this was a small study and relied on telephone interviews years later.

Sinha and Duffy reported higher rates. However, both studies were relatively small and only reported findings out to 3 months. In both, it is difficult to determine whether the pain reported was persistent pain and/or whether procedural pain was included. Furthermore, the Duffy study had follow-up data on only 35 of 48 implanted subjects.

With respect to the high rate in the SUCCES II trial at 3 months, this represents all possible pain events and does not speak to the type, timing, or duration of the pain.

This next slide is busy but is intended just to present a higher-level picture of certain aspects of the study designs with respect to prospective or retrospective, single site or multi-site, and length of follow-up (more or less than 3 months). The IDE studies are on top and separated from the literature and SUCCES II studies by a double line. Outside of the IDE studies, there are a limited number of prospective studies, and they are mainly small, single center, and with limited 3-month follow-up.

Interpreting data related to persistent pain within the literature is made more difficult by other uncertainties or inconsistencies, including the definitions of chronic or persistent in terms of duration, the timing of onset of the pain, how and when the pain was assessed and using what scales, and what types of pain were included or not. For example, some reports may have included procedural pain in the rates and others may not. Some may have included cyclical or intermittent pain such as cramping, dysmenorrhea, or dyspareunia in their definition and others may not have. Many times, the studies did not provide that level of information.

FDA referenced several case reports in our memo which note persistent pain following Essure placement. Although many cited onset of pain at the time of the procedure, there were reports where the patient was asymptomatic following placement and developed pain weeks or even months later. Their duration of pain varied as patients sought attention at various times. Some authors noted difficulties during or immediately after insertion, including malposition or perforation, but others did not.

The case reports frequently noted device removal due in part to the pain. This was done either hysteroscopically or by laparoscopic salpingectomy and sometimes out several

years after insertion. When outcomes for pain following removal were provided, many noted improvement or resolution, sometimes within a short period of time. However, other cases noted only partial resolution, unchanged symptoms, or even worsening of pain.

In the MDRs, pain is the most commonly reported symptom. Over 3,500 reports are coded with at least one item related to pain. Like the case reports, specific details were limited and, when provided, showed considerable variability in terms of onset, duration, and patterns, including whether the pain was constant or intermittent; 341 of the 452 MDRs we have, which note women undergoing device removal, cite at least one pain-related complaint, although it is difficult to know whether the pain was the primary reason for removal. Of those 341 subjects, 135 reported resolution of pain after removal. However, many of the other reports did not provide sufficient information either way, and the actual number may be higher.

In summary, abdominal or pelvic pain, including cramping, were the most common events reported in MDRs. Various types of pain generally appeared at rates of 2% to 5% at follow-up points in the IDE studies. In the pivotal study, recurrent pain occurred in approximately 5%, whereas persistent pain, at least by the Sponsor's definition, was noted in one patient. It is important to keep in mind that patients with chronic pain syndromes, a potential risk factor for post-placement pain, were excluded from enrollment in the IDE studies.

There is limited literature regarding persistent pain following Essure. Several publications reported rates of less than 1%, although one quoted a rate of 4.2%. Many of these studies were retrospective. Limited data were often available in these studies

regarding pain characteristics and associated findings or causes. In addition, issues related to case definitions add to the difficulty in interpreting the data. Multiple individual case reports and reports submitted to FDA suggest persistent pain sometimes lasting months or years and, when the information was provided, often resolving with device removal. However, information from case reports and MDRs cannot be used to calculate rates.

I'd now like to move on to a discussion of vaginal bleeding following Essure placement. In the original PMA, women were asked to assess bleeding patterns compared to usual menses, and changes were reported in 1% to 2% of subjects. At the 5-year follow-up, particularly in the pivotal cohort, higher rates were reported. However, higher rates included heavier flow as well as lighter flow. Rates in the TVU study had been lower. However, no data is being systematically collected asking women to compare bleeding patterns to their usual menses in that study. For all three IDE studies, no control cohorts were included, and as such, it is not possible to gauge what changes may have been part of natural history. In addition, we do not have information related to the use or discontinuation of use of hormonal therapy, which might impact bleeding characteristics.

The graph on this slide shows the rates provided by the manufacturer for several bleeding patterns at each follow-up in the pivotal study. At each visit, approximately 20% of women noted heavier flow when compared to usual menses, 10% to 15% noted lighter flow, 5% to 10% irregular menses, and 5% to 10%, intermenstrual bleeding.

The Sponsor provided information from the pivotal study related to recurrent and persistent symptoms. Between 15% and 38% of subjects experienced recurrent irregular bleeding symptoms, but again, this included lighter as well as heavier flow. And 1.5% of the

pivotal study subjects reported persistent heavier flow at 1 year, and that percentage declined over the study. In addition, less than 1% of subjects had persistent irregular bleeding and/or intermenstrual bleeding throughout the study.

This slide captures our references. And, again, I'm just going to raise a couple of points. The Chudnoff paper represents the 5-year pivotal study, which we discussed on previous slides. Several other studies show similar event rates and also show increases in lighter bleeding.

Mino reported no changes in 857 women who were surveyed. The method of survey was not clear, but it appears to have been done at 3 months. And some, if not many, patients may have still been taking contraceptives at that time.

The citation for Levie is an abstract describing a retrospective cohort of 193 women with Essure and 139 who underwent surgical tubal ligation over a 7-year period at one U.S. site. Although details on this study, including length of follow-up, were not provided, irregular cycles were reported in 30% of Essure patients and 28% of tubal ligation subjects. And menorrhagia was reported in 36% and 46%, respectively.

In the SUCCES II trial, the percentage represents all possible bleeding events and does not speak to the timing, duration, or characteristics of the event.

Here I am again presenting a similar chart as before for pain. And, again, studies on bleeding outside of the IDE cohorts, which includes the Chudnoff paper, tended to either be retrospective single-site reports or short-term, relatively small prospective studies.

Symptoms related to vaginal bleeding were reported in almost 1,600 MDRs and included prolonged, frequent, and/or heavy menstrual bleeding, irregular bleeding,

intermenstrual bleeding or spotting, less frequent or severe bleeding, as well as amenorrhea. However, heavier menses were noted in about half of the MDRs. The reports tended not to provide information related to past bleeding patterns or hormonal therapy use, although some specifically note being placed on hormonal therapy by their physician to address the symptoms. Some others also noted undergoing endometrial ablation or even hysterectomy to resolve or address their symptoms.

Summing up. Although rates of reported bleeding changes were relatively low in the Phase II and pivotal studies at the time of initial PMA submission and in the TVU study, follow-up of the pivotal cohort showed higher rates with time and about one-third of subjects reporting recurrent symptoms.

Few publications have specifically addressed the issue of changes in bleeding patterns, although those that did reported rates similar to the 5-year pivotal cohort.

The lack of control groups in the IDE and literature studies makes the assessment of cause and effect more difficult.

Numerous MDRs describe varying bleeding symptoms, with slightly over half describing heavier flow.

Most of the data reviewed, regardless of source, did not provide information on hormonal therapy use or menopausal status.

Turning now to headaches, which was one of the more commonly reported symptoms in MDRs, like abdominal pain, this is particularly difficult to assess as headaches are a very common symptom in the general population and in women in particular. As seen in this slide, headaches which were deemed to be possibly associated with the device or

procedure have been reported in about 1% to 5% of subjects in the IDE studies, although the criteria used to make that distinction is not known. However, without a control group for such a common symptom, it is difficult to know whether the rate of headaches is higher than in patients without the device.

Literature related to headaches is limited. Yunker's publication found that women with previous diagnoses of chronic pain, including headaches, were at increased risk for persistent abdominal pain but did not report on the rates of headaches postoperatively. Others were essentially case reports at early time points.

Approximately 1,400 MDRs list the presence of headache, including migraines, as a symptom. However, as headaches were often one of several symptoms noted in a given report, additional details were often limited. When information was provided, their frequency of headaches varied considerably from constant every day to monthly or just occasionally. Reports did not typically provide information related to prior headache history or information regarding evaluation and treatment specific to the headache, although a handful of reports did note improvement in headache symptoms after device removal.

I'm going to switch now to allergic or hypersensitivity reactions reported in association with the Essure device. This is a topic which has emerged in the patient community because portions of the Essure inserts are made of a nickel-titanium alloy called nitinol, a material with significant history of use in implantable medical devices, including endovascular implants. As noted in our memo and summarized in the table on this slide, the Essure device itself has been evaluated in terms of nickel leaching, and the release rate

has been found to be comparable to or lower than that of selected cardiovascular nitinol devices.

It is important to point out that cutaneous nickel allergy is common, and up to 25% of women may be affected. We traditionally associate this with a contact dermatitis after skin exposure. However, a systemic contact dermatitis after exposure through other routes may also occur, and some authors have described systemic signs and symptoms, including chest pain, migraines, and respiratory issues, among others. These very potential clinical manifestations make the assessment of a reaction challenging as they can be common symptoms with a variety of causes. The exact mechanism of hypersensitivity reaction to implanted metal devices is not known, and there's no reliable method to identify individuals at risk, although patch testing is sometimes cited in the literature. But since nickel allergy is so common and nickel is present in many products and foods, a positive patch test may be difficult to interpret.

No cases of nickel allergy were specifically diagnosed in the pivotal and Phase II trials, although several dermatological events were reported. In the TVU study, there has been one patient with a metal allergy, although it was mild and resolved without treatment. Several other patients had dermatological events, although no formal diagnosis of an allergic reaction was made.

This slide summarizes literature related to metal reactions. The first two listed were actually reviews of other data sources, including MDRs. However, for both, it is unclear what criteria or set of symptoms each author used to define a hypersensitivity reaction. The remaining two studies, also both reporting very low rates, were both single-site,

retrospective reviews, and again, we are uncertain as to how the diagnosis of allergic reaction was sought or made. In the SUCCES II trial, two subjects have experienced allergic reaction to date.

This table lists four case reports from the literature which describe women who developed dermatological signs from 3 days to 3 months following Essure insertion, three site-positive nickel patch testing after the onset of symptoms, and three note that the patient was at least partly unresponsive to steroids. All four reports note that the patient had the devices removed, with resolution of dermatological symptoms sometimes as soon as 36 hours after removal.

Turning to MDRs, as I noted before, the signs and symptoms which are presumed to constitute an allergic reaction may vary by author or reporter. This makes the classification of MDRs for this event difficult.

For our review, all reports which specifically stated that the patient had an allergic or hypersensitivity reaction with reference to a metal were included, as were reports that mentioned skin manifestations. This is regardless of what symptoms were considered by the reporter to represent the reaction and regardless of any formal evaluation or diagnosis. This resulted in a total of 878 MDRs.

Again, as this was usually one of several issues being noted in a given report, details were often limited. When cited, there was variability in time to onset of symptoms, although some stated it began within hours of insertion. Few provided information regarding formal evaluations, how events were managed clinically, and whether they responded to medical therapy.

The clinical symptoms presumed related to an allergic reaction varied considerably in the reports. And although dermatological signs such as rash or itching were present in some reports, many instead describe systemic symptoms, including pain, headaches, and bleeding. Of the 878 MDRs, 212 describe device removal, although it is not possible to know what degree the allergic symptoms played in that decision. The status of symptoms following removal was provided in 117 of those reports, and all of them noted symptom improvement or resolution following removal.

So with respect to allergic and hypersensitivity reactions, although cutaneous nickel allergy is known to affect a substantial percentage of women, what constitutes a reaction to a metallic medical implant and how to diagnose or predict it is not well defined. Keeping this in mind, the prospective IDE studies have reported few specific metal allergy reactions. Few studies in the peer review literature have addressed this symptom complex, and although they typically cited rates of less than 1%, the data was obtained from retrospective reviews at single sites or was based on MDR or complaint numbers. It is also not clear how an allergic reaction was defined.

A handful of case reports have noted individuals with dermatological manifestations, positive patch testing, and resolution with device removal, suggesting a device-related reaction in those cases. Numerous MDRs cite allergic reactions to the device, including some noting resolution of symptoms with device removal. However, the limited information provided and the variety of symptoms reported to represent the reaction in many can make their interpretation related to cause and effect challenging.

Moving on to insert uterine or fallopian tube perforation during or after Essure

placement, this is a known but potentially significant complication and therefore included in our review.

In the 5-year reports for the Phase II and pivotal studies, uterine or fallopian tube perforation was reported at rates of 3.4% and 1.1%, respectively, with all but one having been noted at the time of the original PMA submission. In the Phase II study, which had the higher rate, five of seven perforations were associated with the use of a support catheter, which is no longer part of the Essure system. In the TVU study, three perforation events have been reported in two subjects to date, both presenting following an unintended pregnancy approximately 1 to 1.5 years after placement.

Due to the number of citations, this slide is busy, but again, the IDE studies appear above the double line, and our cited publications in our memo are below the double line. Many of the literature studies cited rates of perforation at or below 1%. This included several prospective cohorts, although they tended to be single-site experience and often had limited 3-month follow-up. It is also not known if and how perforations were systematically sought in these studies. The highest reported rate of 3.6% was from one of the retrospective studies. To date, in the SUCCES II studies, 30 events have been reported in the combined migration and perforation category, but at this time we can't specifically cite the number of perforations.

FDA cited several case reports or series describing perforations in our memo. The diagnosis of a perforation may have been made any time during or after insertion, with some being made years after the procedure. In some of these cases, patients may have been asymptomatic during some or all of that time. Multiple reports note perforation even

after a prior uncomplicated procedure or even after a confirmation test showing successful placement and occlusion.

Patient presentation at diagnosis usually manifested in one of a few ways, new or persistent abdominal or pelvic pain, asymptomatic women but found after -- a perforation found after evaluation for patent tubes during confirmation, or evaluation of patent tubes following an unintended pregnancy. Some of the cases were associated with intraperitoneal migration or bowel injury, which I will discuss in subsequent sections.

Approximately 300 MDRs describe Essure perforation events, with 90% being diagnosed after the insert procedure. Perforations were diagnosed based on similar presentations noted for the case reports. Although the majority involved perforation of the uterus or fallopian tubes, several described perforation of other organs. This includes five reports in which the reporter alleges that an insert may have perforated the amniotic sac of a pregnant woman, and 12 MDRs which describe bowel perforation, which again I'll comment on in a minute.

In summary, although the Phase II study noted a perforation rate of 3.4%, the pivotal and TVU studies have seen rates of 1% or less. A mix of studies in the literature also cite rates less than 4% and generally closer to 1%.

Numerous case reports and MDRs describe perforations, some diagnosed at insertion but many diagnosed later. Some perforations have been noted in women despite an uneventful insert procedure and even after successful bilateral occlusion assessment. Although some women with perforation present with abdominal or pelvic pain, others are diagnosed only after evaluation of a patent tube, typically when asymptomatic at

confirmation testing or after an unintended pregnancy.

An important set of points to keep in mind is that pain is not always indicative of a perforation. Some perforations may be asymptomatic, and some patients, symptomatic or not, may not undergo laparoscopic evaluation. As such, it may be difficult to detect or confirm a perforation on clinical grounds, and this may, in turn, affect the reporting and calculation of event rates.

I'm going to move to intraperitoneal insert migration, which we attempted to define and evaluate as an issue distinct from proximal tube migration or from expulsion into the uterine cavity, which is a well-described event following the Essure procedure.

In the Phase II study, six cases were reported where at least a portion of the insert was found to be intraperitoneal. However, in only three of these cases were the inserts located entirely within the peritoneal space. In the TVU study, two events of insert migration into the peritoneal cavity have been noted to date.

This next slide summarizes our literature citations with respect to intraperitoneal migration. As with perforations, studies generally reported rates near or below 1%. However, it was not always possible to know whether the definition of migration included cases of proximal tubal migration or vaginal expulsion in addition to intraperitoneal migration. In many of these studies, the migration was noted during confirmation testing, and at least one was associated with unintended pregnancy. The exact location of insert migration was not typically provided.

Most of the publications cited in our review were retrospective single-site cohorts, and prospective studies outside the IDE trials were generally limited to 3 months of follow-

up. Several individual case reports note intraperitoneal migration of an insert or insert fragment. Migration tended to be noted in asymptomatic patients at the time of the confirmation test, although some were also associated with bowel injury and GI symptoms. Although migration is largely felt to be a follow-on to insert perforation, in some cases authors specifically noted that no perforation was present at laparoscopic evaluation, raising the possibility, among others, that the device may have migrated distally.

A few of the reports described local complications or findings at the time of laparoscopy, including bowel perforation or obstruction, adhesions, and inflammation, although the relationship to the device was not always clear. In many reports, the inserts were removed laparoscopically without complications, although in some, intraoperative fluoroscopy was required to locate the insert or fragment. Some surgeons, however, elected to leave the inserts in place if the patient was asymptomatic.

In terms of MDRs, FDA has received 227 reports related to insert migration. About half simply note the abdominal or pelvic cavity as the location, and 25% report migration to or around parts of the bowel. It is possible that some of the remaining reports that describe migration may actually represent expulsion. In cases where the device migrated to or around the bowel, the patient may have presented with signs or symptoms of bowel perforation or bowel obstruction, although this was not in the majority. At least one report noted a surgical ileocecectomy because of a bowel perforation. This case may overlap with one of the literature case reports.

It should also be noted that MDR requirements do not mandate the reporting of an insert migration in which the patient is asymptomatic. Hence, the manufacturer may have

additional reports of migration which are not in the MDR database.

Summarizing intraperitoneal migration, limited numbers of cases have been reported in IDE studies in the literature. However, many of the literature publications were retrospective data collections not necessarily focused on migrations. On the other hand, some may have included cases of proximal migration or expulsion in their definition.

Case reports suggest that intraperitoneal migrations are often asymptomatic and found at routine imaging or during evaluation of suspected patent fallopian tubes. Many describe laparoscopic procedures to remove the migrated device with or without fluoroscopy, although some authors elected to leave asymptomatic migrations alone.

Two hundred and twenty-seven cases of migration have been seen in the MDRs, although it is not certain that all represent intraperitoneal migration. Information regarding these MDR cases were similar in nature to the case reports.

Although migrated inserts may be easier to detect on routine imaging studies than a perforated insert, since they may be asymptomatic, the diagnosis of the event may be delayed or perhaps missed, similar to perforation events.

I wanted to briefly summarize the information regarding reports of bowel injury related to Essure perforation and/or migration. There are three recent case reports which cite small bowel obstruction, perforation, or both, as shown on this slide. All three were diagnosed within a month of placement, and all presented with pain, nausea, and vomiting. Two patients required bowel resection. In addition, FDA has received 12 MDRs citing bowel perforation in association with the Essure device, two of which also report obstruction. Two of the 12 reports describe the need for ileocecectomy, but many represent -- but may

represent the same event reported by two different sources and may overlap with the case reports.

Moving on to device removal, although Essure is intended to be a permanently implanted device, we have seen and heard multiple reports of women seeking or undergoing surgical procedures in order to have the devices removed. As such, we thought this was an important topic to include, and one of our questions to the Panel later today specifically focuses on insert removal.

During the premarket studies, there were five cases of insert removal, as shown on this slide. At the 5-year follow-up, 5.8% of women in the Phase II and 4.2% of women in the pivotal trial had undergone device removal. Our number for the Phase II is different than that presented by the Sponsor earlier as we also included one case of hysteroscopic removal. Removals were largely performed laparoscopically or by hysterectomy, and pain or bleeding were the common issues noted. In the TVU study, 2% of women have had their devices removed to date. Again, pain and bleeding had been the most common clinical scenarios. And for over 63% of the subjects, symptoms resolved after removal.

In terms of literature regarding device removal, the recent Chudnoff report provided additional details on the 15 women who underwent hysterectomy in the 5-year pivotal cohort. The principal reasons included menorrhagia, pain, and dysmenorrhea, although the author stated that only two hysterectomies were due to the Essure device. How that determination was made is not provided.

As we mentioned previously, the Arjona-Berral paper focused on women who sought removal for persistent pain. It did not specifically mention whether additional women in

their cohort had removals for other reasons. But this study did note improvement in symptoms in the seven subjects who were included.

In the SUCCES II study, to date, at least 56 subjects have undergone removal by hysterectomy or laparoscopic tubal surgery to date.

Multiple case reports note insert removal, which we have alluded to in prior sections. Many of these describe laparoscopic removal, including procedures more than 4 years after implantation. Several others noted successful hysteroscopic removal even out beyond 3 months. The more commonly cited reasons for removal were persistent pain and abnormal bleeding, although inserts were also removed following diagnoses of perforation or migration and also at the time of surgical tubal ligation. When outcomes were cited, many noted improvement or resolution of the main complaints. Although many of the reports note no complications associated with the removal procedure, others have noted device fragmentation or difficulty in locating inserts or insert fragments without the use of fluoroscopy.

As I mentioned earlier, FDA has received 452 MDRs describing Essure device removal. These include hysteroscopic and laparoscopic removal, but almost 60% report hysterectomy. Reasons for removal are similar to those mentioned in previous slides but also include presumed allergic reaction, adenomyosis, and prolapse. Only 196 of the 452 MDRs provide additional information on the outcome of symptoms following removal. Of those, about 90% state that the symptoms attributed to Essure either resolved or significantly improved, many times soon after surgery. This includes reports of multiple symptoms resolving, including pain, headache, fatigue, rate changes, and many others.

Conversely, 20 of the 452 reports specifically noted that the pain -- the symptoms did not improve or resolve. Most of those 20 still reported pain.

Summing up device removals, follow-up of subjects in the IDE cohort show rates of approximately 2% to 6%. In the IDE studies as well as case reports and MDRs, common clinical scenarios associated with device removal were abdominal or pelvic pain, vaginal bleeding, perforation, and/or migration. However, in all sources of data, some women underwent removal, and particularly by hysterectomy, for reasons which also included endometriosis, adenomyosis, prolapse, and fibroids, which certainly may have been unrelated to the device. Literature reports tended to note removal via hysteroscopy or laparoscopy, whereas MDRs tended to report removal by hysterectomy.

Regardless of the methodology and the source of information, when symptoms outcomes were reported following removal, many reported significant improvement or resolution.

Finally, I'm going to describe the deaths which have been reported in association with or following Essure placement. As the Sponsor mentioned, two deaths have been reported for subjects in the IDE studies, and they described those. Prior to June 1st, 2015, FDA had received 11 MDRs which described a patient death, although limited information in these makes an assessment of causality difficult in some.

Five reports describe fetal death, which the reporter presumed was due to Essure coils perforating the amniotic sac. We are uncertain if there is duplicative reporting among these cases, and no additional clinical information was provided to assist in the determination of cause and effect.

The remaining six reports describe four unique events: one woman with Group A streptococcal infection 2 days following implant; one woman experiencing cardiopulmonary arrest during insertion, whose autopsy revealed a probable paradoxical air embolism and patent foramen ovale; a woman who died from a pulmonary embolism 13 days after hysterectomy to remove the implants; and one woman who committed suicide, although no additional data was provided.

With that, I would like to introduce Ms. Allison O'Neill from the Office of Surveillance and Biometrics, Division of Epidemiology, who will be presenting some of the effectiveness data that was included in our review memo.

MS. O'NEILL: Good morning. My name is Allison O'Neill. I am an epidemiologist in the Office of Surveillance and Biometrics.

Today I'm going to present a brief summary of the results of FDA's literature review and MDR analysis regarding effectiveness and procedural outcomes. First, I will talk briefly about the Essure procedure in terms of timing and follow-up. Second, I will present a summary of the literature on Essure placement rates. Third, I will present literature and MDR results regarding unintended pregnancy after Essure placement. Fourth, I will present a summary of the literature on patient satisfaction with the Essure device and procedure. And, finally, I will summarize the strengths and limitations of the reviewed literature.

Before I present the results of the FDA literature review, I'd like to highlight a point previously made by Dr. Corrado. Essure is unlike bilateral tubal ligation in that it is a multiple-step method requiring patient compliance with a confirmation test 3 months post-placement. During the 3-month period, the patient is counseled to use alternate

contraception. Therefore, there are three types of unintended pregnancies that may occur after Essure placement. Luteal phase pregnancies refer to pregnancies that have already occurred but are unrecognized at the time of placement. The second type is a pregnancy that occurs either during the 3-month period before confirmation or occurs in a patient who is not compliant with receiving the confirmation test. However, these two types generally do not represent a method failure. The third type is an unintended pregnancy that occurs after an apparently successful confirmation test. This illustrates why reported effectiveness rates may vary by patient compliance and timing of the pregnancies reported.

The effectiveness of the Essure system depends on successful bilateral insert placement. Bilateral placement rates were generally high in the studies reviewed. The overall successful bilateral placement rate, including multiple attempts in studies with more than 50 subjects, ranged from 85.8% to 100%, with most studies reporting rates higher than 90%. Multiple authors reported more than one attempt was sometimes needed to successfully place the inserts.

Factors contributing to unsuccessful placement included:

- Poor visualization of ostia
- Tubal stenosis
- Tubal spasm
- Previous tubal occlusion
- Anatomical irregularities
- Patient discomfort

To increase likelihood of successful placement, some authors have suggested

premedication with NSAIDs and placement during the follicular phase of the menstrual cycle to improve visualization of the tubal ostia as well as decrease the chance of luteal phase pregnancies.

Previous systematic literature reviews have stated that unintended pregnancy is rare following a confirmation test, successful confirmation test, and that the failure rate is comparable to that of other contraceptive methods such as tubal ligation. Many pregnancies after Essure are associated with patient or physician noncompliance or misinterpreted confirmation test results. Failure rates are likely to vary by perfect use versus typical use, meaning that higher failure rates are likely for women who do not receive proper device placement or a confirmation test.

In the literature, confirmation test compliance rates ranged from 28.8% to 100% for different study populations. However, 28.8 was a bit of an outlier from a study of a clinic population in Detroit, and the authors stated that health insurance coverage was a barrier to confirmation testing for many of their patients. All other studies reviewed reported rates of 53% compliance or higher. Health insurance coverage was one of the most important determining factors for patient compliance. For a more detailed discussion of compliance rates and placement rates, please refer to Appendix A of the FDA review memo.

FDA conducted a literature review of the effectiveness of Essure in 2009 as part of ongoing postmarket monitoring and became aware of unintended pregnancies that had occurred in the commercial setting. As a result, a subsequent change to the physician and patient labeling was made in order to include information on these pregnancies.

This is Table 7 from the physician and patient labeling, which is presented in

Appendices B and C in FDA's review memo. The table shows 748 pregnancy reports received directly from the Sponsor, recorded in the FDA MAUDE database, and reported in the scientific literature. The time range is 2001 through end of 2010. Since this labeling change, FDA has continued to monitor potential effectiveness and safety signals as identified by medical device reports, published literature, and other sources as part of regular ongoing postmarket monitoring.

For the recent literature review regarding the effectiveness of Essure, FDA reviewed the peer-reviewed literature from 2002 to 2015, focusing on data from clinical trials and prospective and retrospective cohort studies. In order to better assess effectiveness rate over time after the 3-month confirmation test, articles were assessed regarding sample size and length of follow-up.

This is an abbreviated version of Table 13 from the FDA review memo that includes only studies of more than 500 patients and follow-up of at least 1 year. There were three prospective studies and four retrospective studies, as shown in the third and fourth columns. Each study reported an unintended pregnancy rate between 0.2% and 0.9%. However, many of these pregnancies occurred within the 3-month period before confirmation testing.

Chudnoff et al. described the results of the 5-year follow-up for the Phase II and pivotal trials. As previously noted, there were four luteal phase pregnancies that occurred before device placement and no unintended pregnancies occurring after the confirmation test. However, this study suffered from about a 30% loss to follow-up of the intent-to-treat population.

Two articles reported four pregnancies each that occurred after confirmation testing. Povedano et al. described one pregnancy that occurred 32 months after the Essure procedure. After delivery, laparoscopy showed a unilateral tubal perforation. Details were not given for the other three pregnancies. Veersema et al. described four pregnancies that were each associated with either device expulsion, misinterpreted transvaginal ultrasound, and/or a protocol violation.

Additionally, Fernandez et al. used retrospective French hospital discharge data for more than 39,000 women who received Essure and reported a rate of unintended pregnancy of 0.36% compared to 0.46% observed in those undergoing tubal ligation. However, this and other retrospective data are limited to pregnancies that were associated with the hospital procedure, and thus some pregnancies may have been missed.

In summary, in the highest quality data available, the rates of unintended pregnancy after Essure were low (less than 1%), and more than half of observed pregnancies occurred before the 3-month confirmation testing.

FDA has received a number of medical device reports citing unintended pregnancy. However, due to limitations of the reporting system that have previously been discussed, these reports cannot be used to calculate the total number or rate of unintended pregnancies that have occurred in a commercial setting.

Since device approval in 2002 through June 1st, 2015, FDA has received 337 medical device reports related to unintended pregnancy associated with Essure use. This includes 21 reports that cite more than one pregnancy in a given patient and 69 involving ectopic pregnancy.

Of the 127 MDRs which provided a fetal outcome, there were 76 reported live births, 32 reported miscarriages, and 19 reported elective terminations.

Regarding the outcome of patient satisfaction, satisfaction with the device and/or procedure was generally measured with one or two of the following questions, whether the patient is satisfied with the device or procedure on a scale from 1 to 5 or a Likert scale, and whether the patient would recommend the procedure to a friend.

In the literature reviewed, patients' satisfaction ranged from 89.2% to 100% in six studies with less than 1 year of follow-up. The Chudnoff article, describing the long-term follow-up of the Phase II and pivotal trials, reported that 98% of those not lost to follow-up were somewhat or very satisfied at 5 years. One small Turkish study reported 100% satisfaction at 8 years.

However, the measurement of patient satisfaction has some limitations. First, patients who require device removal due to dissatisfaction or who become pregnant are likely to be lost to follow-up, possibly causing inflated satisfaction rates at the final follow-up visit. For example, in the Turkish study, a patient who experienced an unintended pregnancy during the study did not contribute satisfaction data at 8-year follow-up. Second, satisfaction rating scales varied by study.

The reviewed literature has some limitations as follows. Our presentation has focused on data from prospective, well-controlled studies such as the pivotal and Phase II studies which were used to support the PMA application and supplements. However, many other studies in the literature were retrospective in nature, with variable length of follow-up which may be more vulnerable to study bias. Detailed information about pregnancies,

such as length of time after procedure and occurrence of device migration or perforation, was missing in some articles

Study investigators used different confirmation tests, including HSG, TVU, and/or pelvic X-ray, especially in studies conducted outside the U.S., which may limit comparison between studies. Only one study included a comparison group, and this study was retrospective. And, finally, the measurement of patient satisfaction had limitations, as previously discussed.

The strengths of the available peer-reviewed literature include data from clinical trials as well as real-world use, multiple studies with sample sizes of 100 or more women, and international data including women from North America, Europe, and Australia.

This concludes the section on effectiveness and procedural outcomes.

In summary, Essure has been approved for marketing within the United States and many other nations for over 10 years. Two prospective clinical trials were performed by the Sponsor and reviewed by FDA and its Obstetrics and Gynecology Devices Advisory Panel in support of the approval decision in 2002.

Over the past 2 years, FDA has seen an increase in the number of voluntary adverse event reports related to the Essure system, many coming from women implanted with the device.

In performing our current review of safety and effectiveness data for Essure, which is represented in our review memo and in our talk today, we focused on a number of the more commonly reported issues or concerns and included data and information from a variety of different sources, all of which have their own strengths and limitations.

Later today, the Committee will be asked to review and discuss this data along with other information provided by the device manufacturer and members of the clinical and patient communities. You will be asked to discuss specific safety events, such as the ones presented, and provide recommendations on what risk mitigation steps, if any, might be warranted.

We will also ask the Panel whether any of the issues discussed should be further evaluated through the collection of additional preclinical and/or clinical data.

Finally, you will be asked to consider the current safety data in relation to the device's effectiveness and to provide us with your overall assessment of the risk-benefit profile of the device.

We appreciate your time in helping us review and interpret the current data related to the Essure system and look forward to your discussion and recommendations later this afternoon.

This concludes FDA's presentation. Thank you.

DR. IGLESIA: I would like to thank the FDA for their presentation.

Does anyone on the Panel have a brief clarifying question for the FDA? And please remember that the Panel may also ask the FDA questions during the Panel deliberation session this afternoon.

I'll start with Dr. Stubblefield.

DR. STUBBLEFIELD: A comment on the first FDA presentation comparing LARC methods to hysteroscopy. I'm very fond of LARC methods, but I have to point out that the expulsion rate for both IUDs is more or less 5% per year, and that goes on year after year.

Also removal for pain and bleeding is comparable and again goes on for year after year. The etonogestrel implant has about a 20% removal for excess bleeding in the first year. So if you're comparing the methods, there is -- it's kind of hard to keep people on the LARC methods for 5 or 10 years. It takes a lot of love and care and repeat procedures and so on.

DR. IGLESIA: Thank you.

Dr. Coddington.

DR. CODDINGTON: Thank you very much. And I'll thank the FDA for their review, complete review of the different aspects of the device.

For all of them, the question comes up on the MDRs, that there is not specific data available to allow us to get some insight into the process. And as Dr. O'Neill said, there was 53% compliance and then 30% lost to follow-up. So my concern is, is that there's a lot of information in that dataset. It was not clear to me whether they had the opportunity to look over the data from the manufacturer, stating why there were dropouts or why there was lack of compliance. And so I think some of that may give us a better insight, particularly when Dr. Yustein related to the fact that there was bowel injury, for instance, that occurred within a month of the placement of the device. Your thoughts from the FDA group?

DR. IGLESIA: Dr. Yustein.

DR. YUSTEIN: So I'm sorry, can you rephrase? Is there a specific question that you'd like us to try to address?

DR. CODDINGTON: Well, I guess the question is, is do you have access to any of the -- I'll call it raw data from the industry that allows insight into some of these dropouts or

information, you know, so that you might have a better explanation or understanding of our process? I mean I know the MDR process has its limitations. I appreciate that. But I guess the simple thing is do you have any access to the raw data from industry?

DR. YUSTEIN: So I guess I just want to clarify. So the raw data in terms of the MDR events or the raw data from the clinical trials that they conducted or both?

DR. CODDINGTON: Let's just say both, and I'll let you take from there.

DR. YUSTEIN: Okay. So I mean, it's two different topics here. So in terms of medical device reports, the majority of time -- Essure being an exception, the majority of time the reports we get mainly come from manufacturers. We typically say that about 95% or over 90% of our MDRs come from manufacturers. With Essure it's a little different. As you saw in one of the graphs I showed, we have a much higher percentage of voluntary reports. The manufacturer reports that come in, they are expected to do an evaluation of the event and include that information in the MDR that they send in.

They also have the ability to send in what we call supplements to the MDRs as they learn additional information, because manufacturers are supposed to send in an MDR within 30 days of learning of the event. So that doesn't always give them the opportunity to know everything that happened within 30 days. So it's not uncommon for them to then submit additional information as an MDR supplement for that event. Within the MDR there are different sections of an MDR document, and there are sections for narratives or conclusions that the manufacturer based their evaluation. So they do give that information. Do we have all the information that they did in terms of their investigation? That would be in their files.

In terms of the -- I'll defer to the ODE folks. So your other question is in terms of why patients may have dropped out of clinical studies. Does anybody want to handle that one? Can we kind of discuss that after lunch maybe? Is that okay?

DR. CODDINGTON: That would be great. Thank you for the clarification, really, for all of us.

DR. IGLESIA: Thank you.

Dr. Seifer.

DR. SEIFER: Partially as a follow-up on that, in terms of -- it's been presented by multiple people that this is a three-step mandatory process and that when Bayer presented their information about pregnancies occurring, they said all of them occurred before the 3-month confirmation test. And I think Ms. O'Neill was talking about half of the pregnancies occurring before the confirmation test, and she also stated this broad range of compliance rates between 28% and 100% in the literature. So can we get some more information about why that range is so broad? She mentions health insurance was an important factor. Can you give us some information about that?

DR. YUSTEIN: Give us one second.

(Pause.)

DR. YUSTEIN: We have a backup slide, and we'll try to pull that up.

DR. IGLESIA: Would it be easier to do this after -- for the afternoon session?

DR. YUSTEIN: We can do it after lunch if you just want to give us some questions that you'd like us to --

DR. IGLESIA: That way we'll -- but I'll remember it.

Dr. Myers. We'll take two more questions from Dr. Myers and Dr. Milner.

DR. MYERS: Yeah, I just wanted some clarification about the adverse event of pain. And I believe I heard a statement made that patients with preexisting pelvic pain were excluded from the IDE studies. Was that correct? So therefore everything presented in what we've been seeing is post-procedure pain, not preexisting and recurrent.

DR. YUSTEIN: Right. What we presented -- what was that?

(Off microphone comment.)

DR. YUSTEIN: Right. For the IDE studies, patients -- one of the exclusion criteria was chronic pain. Right.

DR. MYERS: Thank you.

DR. YUSTEIN: Right.

DR. MYERS: Thank you.

DR. IGLESIA: Dr. Milner.

DR. MILNER: Just sort of a general question that derives from a specific point that was made, which is that in the Phase II and pivotal studies, with respect to metal allergy and hypersensitivity, it says there were no allergic reactions, and then it says there were four reports of itching, hives, rash, or eczema. And so I guess my question, first of all, is what is that if it's not allergy?

And then the second question is what are the specific standards that are used to define what allergy and hypersensitivity is, and were the same standards applied for these studies? Is there a specific standard that is common to all trials like this?

DR. YUSTEIN: So thank you very much for that question, Dr. Milner, and I think that's

one of my questions to you guys as well. When we were presenting our data, we tried to be very careful in terms of how things were coded. So certainly one of the reasons why I listed those dermatological events was because, even though they were not specifically listed under the MedDRA coding or a coding as an allergic reaction, certainly some may interpret it as an allergic reaction.

So I was just trying to give that data, and the interpretation is certainly up to you. I think one of the things I tried to point out during my presentation is that reading through a lot of the literature, it is very unclear in terms of how people defined what is an allergic reaction or a hypersensitivity reaction, and I don't think it's possible to know in a lot of literature how they defined it. They would just come out and say the rate of allergic reaction was 0.04%, but I don't know how they sought it.

DR. MILNER: I guess my question is, in an IDE --

DR. YUSTEIN: Okay.

DR. MILNER: -- is there a standard for reporting? When you get a symptom, is there a standard for what -- specifically with respect to allergy and hypersensitivity or if you see that symptom it gets listed under there and that's --

DR. YUSTEIN: And I think every IDE -- and I'll let the ODE folks talk to this. Every IDE study and protocol probably has distinct -- you know, there's no standard definition, I think, that we use across every IDE study. And I can't tell you, in this particular one -- maybe we can look that up -- if and what that definition was. But oftentimes the individual study may define it for that particular study, but we can try to find out for you if and how it was described in this particular one.

DR. IGLESIA: Okay, thank you very much.

We will now take a 10-minute break, but I encourage all Panel members to write down any questions that we may have so we can discuss them in the afternoon. And, Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members inside or outside of the audience.

And, Ms. Craig, we will resume at?

MS. CRAIG: 11:26.

DR. IGLESIA: 11:26.

(Off the record at 11:16 a.m.)

(On the record at 11:42 a.m.)

DR. IGLESIA: Would everyone please take a seat? Thank you. We will now proceed with the first portion of the Open Public Hearing. For the record, all Panel members have been provided written comments received prior to the meeting for their consideration. During the Open Public Hearing, public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Craig will now read the Open Public Hearing Disclosure Process Statement.

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that

you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. IGLESIA: The FDA and this Panel place great importance in the Open Public Hearing process. The insights and comments provided can help the Agency and this Panel in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of the goals today is for this Open Public Hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the Chairperson. Thank you for your cooperation.

Now, each registered speaker will be given 3 minutes to address the Panel. We ask that each presenter speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting. The Panel appreciates that each speaker remains cognizant of their speaking time.

Will Speaker No. 1 please step up to one of the two floor microphones on the floor? Or if you are unable to do so, a microphone can be passed to you. Please state your name and any organization you are representing for the record. Thank you. Correction, the first speaker is the first video.

(Video played.)

MS. RUTTER: My name is Lori Rutter. I was diagnosed with MS late in '97. Essure was implanted December of '03. There was no nickel test. I was told it was no risk. It was a good option for me with no surgery. I had trouble within a few months with severe pain and heavy bleeding, et cetera. The doctor moved out of the state soon after. Over the next year, my disease progressed. I stopped driving in a week. I had to use a wheelchair. And then in 2011, I needed to use a power chair 24/7. Now I struggle to stand for 15 seconds. Many have MS in my area, many not in wheelchairs, and virtually none who have been on an MS drug since the beginning like me. I thought my body responded inevitably to this device being implanted. Now I understand completely.

After further research, I learned of something called FBR, or foreign body response. The immune system is intended to be our protector. When the immune system finds a foreign body, it destroys and eliminates it from the body. However, in autoimmune diseases, it actually attacks itself rather than the foreign substance, thus creating a perfect storm to wreak havoc in your body, like it did with me. Having an underlying autoimmune disease is a counterdiction for mesh, according to some mesh manufacturers to the doctors.

Cancer researchers know there are links between chronic inflammation and development of cancer. Autoimmune researchers know there are links between autoimmune diseases and the chronic inflammation. Some surgeons know there are links between implants and autoimmune disease. Degradation and products of PET are considered toxic. Substantial testing was not done. PET has been identified to make cancer cells multiply. Inflammation can become chronic. Cell mutation can result and create an

environment that is conducive to new development of cancer. So much more, but bottom line, this is an inflammatory device that is worsening and creating autoimmune disease and cancer at the expense of women and families everywhere, not to mention all of the other issues. I was not given the proper information to make an informed decision. PET fibers in Essure causes chronic inflammation, which in turn caused my body to react. Long-term nickel exposure is toxic.

I urge you to recall this device. Not everyone will get cancer and develop autoimmune disease, but there are certainly those of us who do and deserve the right to know. My desire to avoid surgery could have killed me with malignant cervical cancer. It did change my MS. I was a functioning adult living life with a chronic illness until Essure. All medicine stopped working and the disease changed course. I have not been a mother or wife for a long time, and because of this fact, I cannot live without assistance. Essure was the worst decision I ever made.

Thank you.

DR. IGLESIA: Will Speaker No. 2 please come up to the microphone? State your name and affiliation. Krystal Donahue, come on up.

MS. DONAHUE: Currently there are over 7,000 Essure adverse events filed with the FDA. A study I co-authored was recently published in *Pharmaceutical Medicine*. It analyzed adverse event submissions from 1,349 women received via the MedWatcher app over a 7-month period. One of the major findings was that 77% of these women reported serious events, including hospitalization, disability, and permanent damage after implantation. One patient reported three times before an investigation was completed. One's directly to

Conceptus, one's through MedWatcher app updating to report surgeries and a diagnosis of cancer, and the third time her doctor filed a report. The result of the third complaint was their concluding that since no product was returned, we were unable to perform an investigation.

As a voluntary reporter, I am not an extreme case. I did not get pregnant, develop life-threatening complications, or get cancer. My coils did not migrate or perforate. I did, however, endure physical pain and mental anguish for 2 years after being implanted with Essure. My major complications were abdominal pain, painful sex, extreme fatigue, joint pain, rashes, and abdominal swelling. I visited a doctor more than 20 times in the 2 years wearing Essure. I had multiple blood tests, four ultrasounds, a CT scan, pelvic X-ray, a month of physical therapy, a cortisone injection, exploratory laparoscopy, and Lupron to rule out endometriosis. My primary care doctor finally told me that if I could not convince an OB/GYN to remove them, he would refer me to a general surgeon who would.

I was finally able to find a doctor at a small practice who would discuss Essure removal. After an internal exam where I convulsed off the table in pain, he agreed that they needed to come out right away. I had a hysterectomy on my 37th birthday. I thank Dr. Lacher, Dr. Adashek, and GBMC for freeing me from the pain Essure caused. I wish I could thank the FDA, ACOG, or Bayer for helping, but they are simply failing us. Focus on profits.

Despite the thousands of women harmed and despite all the data presented here today, Bayer and the FDA have difficulty seeing the causal relationship between Essure and our health due to limited data. Adequate studies should be required before marketing a

device that is meant to be worn for life. This is totally unacceptable. It is my opinion that premarket approval should be revoked on this product due to continued patient harm from the procedure and wearing the device over our lifetime.

Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 4, please step up to the microphone. State your name and affiliation. Elena. Elena Mendez.

MS. MENDEZ: My name is Elena Mendez. I am from -- I'm sorry. Hi, my name is Elena Mendez, affiliated with Essure problems. I would like to start by thanking you for giving me this opportunity to speak. I felt it was important for me to be here and travel from New York to share my experience I had with Essure.

I was implanted with Essure in February 2008. My doctor highly recommended it to me. He felt I needed permanent birth control due to the fact I previously had, 3 weeks prior, NovaSure ablations. It was described to me as soft, flexible inserts, no hormonal side effects. And the biggest selling point to me at that time was no down time. I was working as an ER nurse, I had two small children, and this was an optimal situation for me. I was told that my sensitivity to nickel and my previous piercings that rejected multiple times were not an issue for me because Essure was not made of the same nickel that was in costume jewelry. I was informed that I would need an HSG or a sonogram within a few months. When I called the facility to schedule my HSG, I was informed that I could not have the HSG because I had a NovaSure procedure done prior. I tried for several months. I tried several facilities to no avail, and no one would do this HSG for me.

Multiple sonograms were done over the years due to my complaints of pelvic pain, bladder pain, pressure, and painful intercourse. The sonograms were performed in my doctor's office and led by my doctor, and I was informed that Essure coils were within normal limits and no other pathology was noted. Well, I was told repeatedly that Essure had no side effects, they don't move, and there's nothing wrong with me. I lived in constant pain. My quality of life was severely diminished. Chronic pain became my norm every day. I could not have sexual intercourse with my husband as the pain was excruciating. This negatively impacted my marriage. I could not be a mother to my children that they deserved or the mother I was before Essure was implanted. I couldn't even be the ER nurse I was before Essure. Most nights I was at work taking care of patients, holding my own pelvic area, appearing as if I myself was in need of emergency medical services.

Every aspect of my life was affected and altered in so many ways. After years of enduring pain, another doctor ordered a pelvic-abdominal CAT scan. My Essure coils were not in the correct location. Upon laparoscopy and hysteroscopic, my right Essure coil was found totally covered in scar tissue and buried in my endometrial cavity. The left coil was barely in my fallopian tube. And while Essure and my fallopian tubes have parted ways with me, I am left with adrenal and kidney issues and memories of the woman, mother, and nurse I was before I had Essure implanted. I count too, and I am real.

(Applause.)

DR. IGLESIA: Thank you.

Speaker No. 5, please state your name and affiliation.

MS. FARMER: My name is Chandra Farmer. I have no financial conflict of interest

with Bayer or Essure.

I chose Essure for birth control when my last child was born in 2012. Three weeks after implanting, I experienced heart palpitations, weight gain, hot flashes, migraines, insulin resistance, nickel and chemical allergies, psoriasis of my hands and my vagina, interstitial cystitis, and 37 other symptoms. Soon I became so tired I was sleeping 18 hours a day. My neurological team was stumped. I had all the symptoms of narcolepsy. I even tested positive for the narcolepsy genotype but never once tested positive for narcolepsy in multiple sleep studies. Their last words to me were go home, get a good night's sleep, and see a psychiatrist. Those words devastated me. They were the specialists. They were supposed to help. HLA genotyping should have been part of the clinical studies.

Each of my narcolepsy symptoms were scary in their own right, but the narcolepsy symptom cataplexy was debilitating. Cataplexy is defined as loss of muscle tone upon emotions while being completely conscious. My cataplexy was mostly full-body attacks. I would fall to the ground completely paralyzed and lay there for up to 8 minutes at a time, and I could do this 20 times a day. Living with cataplexy was a daily struggle. I had to stop driving, be mindful of my surroundings because of falling, and even then found myself in the ER with concussions. I became depressed because I literally had to stop feeling. I was captive in my own body.

I remember a terrifying instance where I had swung too far forward, and I thought I was going to die of suffocation, and all I could do was scream inside my own head for help. After 1 year of having cataplexy, it became normal for my very young children to tell strangers, it's okay, my mom does that sometimes. There is nothing more heartbreaking in

this entire world than having your babies have to be your caretaker or your advocate.

I found Essure problems online. I took the information to my new OB, and he agreed to a hysterectomy on August 29th of last year. It has been 1 full year since surgery, and I have not fallen down with cataplexy since. Not once. All of my other symptoms have vanished. The only thing that lingers are my new autoimmune problems.

There are many, many more women out there with neurological problems like me. I have personally talked to dozens who have said they have the same symptoms and just didn't know what to call it. They are out there, and they are real. I had the most horrific experience with Essure. I had the coils removed during a surgery I was terrified to have. But now I'm living instead of existing. You all can call it what you want, but we call it Essure.

Thank you for your time.

(Applause.)

DR. IGLESIA: Thank you.

Speaker No. 6, please state your name and affiliation.

MS. TATE: Good morning. I'm Lisa Tate, Interim Executive Director of Healthy Women, the nation's leading online women's health resource. We are a nonprofit organization that receives funding from a wide range of sources. I understand that we have received funding from Bayer in the past. I have no personal financial interest.

Prior to joining Healthy Women, I was CEO for a long time for a national patient organization for women with heart disease. During my tenure there, I saw the development of the vast array of online options for women to educate themselves about their health.

The Internet and sites like Healthy Women have provided unparalleled opportunity to empower patients and consumers. For example, today, when we go to our physician, we often walk in with a list of questions that we've gotten from research on the Internet. This absolutely does result in better care.

But along with these positives there are also negatives, particularly with the explosion of social media. My organization had a 15,000-member patient community. However, even though the community had policies against giving medical advice, it was uncommon for women to follow this. One example was women who had experienced very serious side effects from cholesterol medication and advised women not to take that, even though this is literally life threatening for a woman with heart disease. And there are many options to reduce the side effects, like taking -- and these decisions should be made with a woman in consultation with her doctor.

Today we're talking about birth control, which is an important choice and one of many very important life decisions that women have to make along their personal healthcare journey. Yet, not every woman needs the same type of birth control. Birth control is not one-size-fits-all, and all women need scientifically sound information to guide them in their decision making. Having access to birth control options that fit a woman's individual needs is important, particularly if she has completed her family and is looking for a permanent solution for family planning. This is a big decision in a woman's life. The cornerstone of this level of decision making starts with a conversation between the patient and the healthcare provider. Women need to know what questions to ask, and healthcare providers need to be at the ready with the answers.

As an educational source for the more than 5 million women who annually visit healthywomen.org, we understand the importance of availability of reliable, medically sound scientific health information. We advocate that women should have access to the full array of contraceptive options approved by the FDA and that a woman's choice of birth control method, or any other major healthcare decision, should be made in collaboration with her healthcare provider. This hearing today will provide important information for both women and their healthcare providers.

Thank you.

DR. IGLESIA: Thank you.

Speaker No. 7. Please state your name and affiliation.

DR. GARIEPY: Good morning. My name is Dr. Aileen Gariepy from Yale School of Medicine, Department of OB/GYN.

Next slide, please.

I am a trainer for the Nexplanon reversible contraceptive.

Next slide, please.

Today I'd like to focus on effectiveness. The introduction of Essure in 2002 was very exciting for women and doctors. Essure was publicized in popular women's magazines and focused on office procedures and avoiding anesthesia.

Click. Can I get a click? Can you advance? Thank you. Natural barriers -- and click -- and superior effectiveness. Click, please.

I was excited to be a doctor offering Essure, until I found that the clinical reality did not reflect the published data. Click. Click. So I looked more closely at the published data.

The major disadvantage of Essure is that it's a multi-step procedure, which means there are multiple opportunities for a problem. I found that Essure publications and advertisements focused on the best-case scenarios of effectiveness -- click; click, please -- if everything went perfectly. And it excluded women with unsuccessful steps. If you could click the next field. And also excluded women who got pregnant at each step. If you can click again. Unfortunately, as we know, few things in life are perfect, and women and doctors want to know realistic chances of each step being successful. So that was the analysis that I did. Click.

My colleagues and I performed an intention-to-treat analysis incorporating all available published data in the peer-reviewed literature, which mostly -- which more closely reflects real-life experience. Click. And what that showed is that 85% of women attempting Essure were sterilized at 3 months. Is 85% good enough? That depends. With laparoscopic sterilization, 99% of women who attempt the procedure are sterilized. And this doesn't even take into account the risk of pregnancy.

So I performed a second intention-to-treat analysis. Click. Again, based on all the published data in the literature at the time that it was published, there was -- sorry, click -- a 10-times-higher risk of pregnancy with Essure at 1 year than there was compared to the CREST data for laparoscopic sterilization. Click, please.

When we talk about contraception, we typically report on perfect and typical failure rates at 1 year, but currently we do not report that for female sterilization. Click. We can and should differentiate -- please click -- and advertise what the perfect versus typical rate is for Essure. Please click.

The good news is, is that Essure may still have promise. It's still not incisional. It can be performed in an office. Laparoscopy can be avoided and maybe even general anesthesia. However, we are missing key pieces of data, and more data is needed. Click. We need transparent reporting of the data that we currently have -- click -- including mandatory pregnancy reporting of all pregnancies to a national, impartial data and safety monitoring board. Please click. We should be talking about typical failure rates, not perfect failure rates. Please click. And I do believe it's time for CREST 2.0 and update a national multi-site collaborative review of sterilization. Our CREST data is now 30 years old. We need a prospective cohort that directly compares Essure and laparoscopic sterilization, measuring all clinically meaningful outcomes, including side effects and repeat surgery. We need an intention-to-treat analysis, prompt publication of data, and then we can know how sure Essure is.

DR. IGLESIA: Thank you.

DR. GARIEPY: Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 8, please state your name and affiliation.

MS. HOWELL: Good morning. My name is Rebecca Howell, and I have no ties to Bayer. Thank you for taking the time to hear our case.

After my third child was born, heart complications required either my husband or I to become sterilized. We saw Essure advertised as a perfect product for a new mom scared to conceive again. I was implanted with Essure in August 2011, and in November 2011, I was told I had been made sterile and the placement was perfect. This perfect placement

was also confirmed by several CT scans, X-rays, and ultrasounds over the course of the 2½ years I had Essure in my body. This placement did not prevent the long list of symptoms that appeared immediately after placement and the months and years after: back pain, joint pain, increased migraines, weight gain, struggle to lose weight, bloating to the point I looked pregnant, chronic fatigue, food sensitivities, heavy painful periods, urinary tract infections, monthly yeast infections, painful intercourse, hair loss, elevated CRP and sed rate, and nickel sensitivities. I had to stop wearing my wedding bands because of the nickel content in the white gold.

These symptoms got so severe I had to educate my home-schooled children from my bed. There were days when I would not get up out of the bed except to crawl to the bathroom in tears. I felt less like a woman, less of a human. I became depressed. It was only my faith in God and my loving family that kept me from ending it all.

After finding a group of women with similar issues, I began my struggle to find a doctor who would listen to me. The doctor who implanted my Essure device refused to see me. Emergency room doctors thought I was a drug addict. University of Florida OB/GYN attendings had no idea what to do with me. It wasn't until I had proved that I had developed a Level 2 nickel allergy on a scale of 0 to 3 after having the implants put in that I had a doctor listen to me.

On December 20th, 2013, my cervix, uterus, and fallopian tubes were removed. My coils were handed over to me intact. They had not migrated out of my tubes or broken. My symptoms improved after removal. Yet, there are side effects of Essure and hysterectomy that may never go away. My story is simple and by far not the worst story you're likely to

hear today. Yet, in my eyes, it proves that even with perfect placement and no complications of breakage or migration, that Essure wreaks havoc on the lives of women. Had I opted for a simple tubal ligation, I would not have gone through this. My children and husband wouldn't have to watch me in misery. I would have an intact body and not deal with the ramifications of a hysterectomy at 30 years old.

The only, only acceptable solution for the women suffering, the women and children who have died, the families torn apart, and the physical, mental, emotional, spiritual, and socioeconomic stress on our lives is for Essure's premarket approval to be revoked, Essure to be permanently recalled, and for the Bayer company to be held responsible for the damage caused by their faulty product.

Thank you for your time.

DR. IGLESIA: Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 9, please state your name and affiliation.

DR. JAMSHIDI: Good morning. My name is Roxanne Jamshidi. I'm an OB/GYN. I'm an Associate Professor of Obstetrics and Gynecology at George Washington University. I'm also the director of the division of general OB/GYN there, but today I'm actually here on behalf of the American College of Obstetrics and Gynecology. I have no financial conflicts of interest to disclose.

ACOG is a national medical organization representing nearly 59,000 OB/GYNs and partners in women's health. On behalf of ACOG, I thank the FDA for its attention to the safety of hysteroscopic sterilization with Essure as the health and safety of patients is of

utmost importance.

Contraception is an essential part of women's health. The majority of women will use birth control at some point in their lives. Female permanent contraception or tubal occlusion, commonly referred to as sterilization, is one of the most popular methods for women. Six hundred thousand tubal ligations are performed each year in the United States.

ACOG considers it essential that less invasive tubal occlusion options, like Essure, be made available to women because it is critical that women have a choice when it comes to contraception.

As you know, female permanent contraception can be performed through two different routes, abdominal or transcervical. At this point Essure is the only technology available to perform a less invasive transcervical tubal occlusion which does not require general anesthesia and can be performed in a physician's office rather than the general operating room. All medical procedures carry risks and benefits, and no single approach is right for everyone. However, a woman's coexisting medical conditions, including obesity, cardiac or pulmonary disease, may make a less invasive approach a safer sterilization option. Additionally, because the hysteroscopic approach does not require entry into the abdominal cavity, major morbidity associated with general anesthesia and abdominal surgery can be avoided.

In order to improve the use of hysteroscopic tubal occlusion in the future, we ask the FDA to take steps toward obtaining more high-quality data on both its safety and efficacy. We know that there are tools available to the FDA and the medical community to better track and understand Essure use. Postmarket surveys and studies, comprehensive patient

registries, and unique device identifiers will allow us to evaluate not just a patient's insertion experience but also her long-term response and wellness, including the potential side effects and incidence of those side effects.

We know that permanent contraception is of life-long importance to women and their families. We want to understand the positive and negative impacts of this choice. This involves improving the data available to women, to physicians, and to the FDA itself.

Moving forward, ACOG would be happy to continue to advise the FDA on the importance of contraceptive choice and on the information that will help us make appropriate decisions in the future.

Thank you.

DR. IGLESIA: Thank you very much.

Speaker No. 10. Michelle Garcia. Ms. Garcia.

(No response.)

DR. IGLESIA: Okay, we're going to skip on down, then, to Speaker No. 12. Sarah. And please state your full name and affiliation.

MS. SORSCHER: Before I begin my presentation, I'd like to ask permission from the Chair to present at the podium where I can have access to a remote to move my PowerPoint through.

DR. IGLESIA: Can you move over to the microphone on the -- to your right? Oh, I'm sorry, your left, my right. So we do have an advancer on that microphone.

MS. SORSCHER: Okay. And I'd also like my full 3 minutes restored, if that's possible. I'm not seeing my presentation up yet. And now I'm trying to get this clicker to work.

There's no -- over there?

UNIDENTIFIED SPEAKER: Here it is.

MS. SORSCHER: Okay. This is going to be challenging. Well, if there's no alternative, I'm going to ask to verbally move the slides forward. Okay.

Good morning. My name is Sarah Sorscher. I am a researcher with Public Citizen's Health Research Group. I have no conflicts of interest.

Slide, please. Oh, go back, please.

Today's meeting was called in response to a large increase in adverse event reporting driven largely by patients. I won't dwell on these reports because so many of those patients are here today.

Slide, please.

Instead, I will focus on safety issues in the two premarket trials conducted by Conceptus, Essure's prior manufacturer.

Slide, please.

The total number of patients experiencing an adverse event related to pain in these trials was not reported, and pain severity was also not reported systematically. And even these results show that nearly 1 in 10 women experienced back pain in the first year, and severe pelvic pain and cramping occurred in at least a small but notable minority of women.

Slide, please.

Strikingly, removal rates in the premarket trials were over 4%, and the main reasons for removal involved safety issues, including bleeding and pain.

Slide, please.

The 5-year follow-up reported apparently glowing patient satisfaction and lack of persistent pain.

Slide, please.

Yet, this extension study had many flaws, and points involving comfort and satisfaction with the device were vague and subject to biased interpretation. Again, severity of pain was not reported. And in the follow-up, pain outside the pelvis, including low back pain and abdominal pain, were also not reported, although they were collected by Bayer -- by Conceptus. Finally, the definition of persistent pain or pain recorded at every visit was too rigid, resulting in exclusion of patients with chronic recurring pain.

Slide, please.

To illustrate some of these problems, I have data from a subject enrolled in the pivotal trial, Kim Hudak. She is testifying today and has given permission to use her name.

Slide, please.

Kim experienced long-term debilitating pain and other symptoms that began soon after receiving the Essure implant and largely resolved after the device was removed via hysterectomy after the trial. Kim reported this pain, yet her physicians insisted that it was unrelated to the device, and her forms were consistently marked with ratings of excellent and very satisfied.

Slide, please.

Here's the summary. Her comfort and satisfaction appeared uniformly high in spite of reports of severe pain. And because pain was not recorded at every visit, her long-term pain would not have been considered persistent. Pain severity and other symptoms, such

as 80 pounds of weight fluctuation, were not reported at all in the published results.

Slide, please. And slide, please.

The patient testimony today makes clear that Kim's experience is not an isolated one. But even if such stories were rare, and we do not believe they are, a device that causes this level of debilitating long-term pain should not remain on the market. Essure's benefits do not outweigh its risks, and it should be withdrawn.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 13. And please state your name and affiliation as well.

MS. HUDAK: Hi, my name is Kim Hudak, and I have no affiliations.

I was part of clinical trials for Essure. In 2000 when I signed up for this, I was really excited to be a part of this revolutionary product. It's something that I wanted for all women. It was my understanding that clinical trials for a new product were designed to test the safety and efficacy of a new product in a controlled environment where all possible side effects would be recorded. Within a few weeks of the procedure, I was experiencing a constant sharp pain in my left hip. I was also suffering from debilitating fatigue and severe PMS symptoms. By my 3-month follow-up, I was in nearly constant pain and suffering from extreme migraines.

When I spoke to the clinical trial nurse and my doctor about these symptoms, they made it clear that they did not think that the symptoms were related to the device. They recommended that I seek help from outside doctors, my primary gynecologist and other specialists. When I would mention my procedure to these other specialists, they didn't

know how to help me. I was terrified, and my health was rapidly declining, and no one had any answers for me.

The clinical trial questionnaire didn't allow for accurate reporting of all symptoms. The questions were presented in a very leading way. For instance, the question, rate your comfort of wearing the device, I was told specifically that if I can't definitely feel that coil inside of me, I should rate it as excellent. And another question was rate your satisfaction with the device. For this question I was told that because the product did exactly as promised and I did not become pregnant, I should also rate that as excellent.

With each passing month, my symptoms became more severe. With each clinical trial follow-up, I was told, I'm sorry, your symptoms are just not related to this device. Within 12 months of placement, I developed pain throughout my entire body, odd rashes, constant infections, and minor neurological issues. By the time I had a hysterectomy in 2013, I had cognitive problems, slurred speech, widespread pain and swelling. I couldn't work and can barely function as a mother.

I have slides and, you know, I just feel that -- they're not here. There we go.

As you can see by my medical records, many of my answers regarding pain were crossed out and replaced with answers showing I was satisfied. It's unclear what was actually reported back to the FDA, but what is clear is the severity and diversity of my symptoms were not reported.

Since removal in 2013 and another surgery to remove a remaining piece of the coil in 2014, most of my health issues have improved or are completely gone. That's a small consolation to the almost 15 years that I lost. Please don't let this happen to other women.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 14. And then just state your name and affiliation.

MS. AVINA: My name is Gabriella Avina, and I have no affiliation with Bayer. I want to thank you for this opportunity to be heard for a second time.

In July 2002 I stood before you in Washington, D.C. to express my support for Conceptus and the Essure device. I was on the panel to request FDA approval for this new, revolutionary device. I am here today, almost 13-plus years later, to say I was wrong. So please listen carefully to me and to these women with me today. Time has changed my thoughts, my beliefs, and most importantly my health.

I am a registered nurse with a master's of science degree in women's health nursing and an M.B.A. I was involved in the clinical trial at both a professional and personal level. I became a part of a clinical trial after my third child was born with an IUD and my husband's vasectomy grew back. I assisted in the placement of the devices in the operating room with Dr. Don Galen, and I became a clinical trial participant in October 2000. Because of my experiences both as a clinician and a patient, I was asked by Conceptus to speak at the annual AAGL convention in San Francisco and share these experiences. This began a professional relationship as a spokesperson for Conceptus that lasted through 2008.

I traveled the country speaking to large groups of doctors, nurses, patients, and Conceptus employees. I managed the link on the Essure website known as Ask Gabby, where I answered thousands of questions regarding the product, adverse events, fears, concerns, and general information. All of that information was recorded, tabulated, and

returned back to Conceptus. As I became the face of Essure women, my health was in a grave tailspin, and I had failed to connect the dots.

In April 2001, not 6 months following placement, I was diagnosed with Hashimoto's thyroid disease, whereby the body attacks the thyroid believing it to be foreign. The only foreign objects in my body were the Essure coils. In 2003 I was hospitalized with an acute onset of immunologic thrombocytopenic purpura with a platelet count of 4,000. I was hospitalized for nearly 2 weeks with several transfusions, treatments, and tests. My children were not allowed to hug me for fear of causing a bleed. One year later, after several hospitalizations and complications, I was started on chemotherapy to suppress the bone marrow production of these bad antibodies. I finally reached a safe zone and remission in late 2005. But during this time, I lost my job due to my illness.

In 2007 I was diagnosed with another autoimmune disease, celiac disease, a gastrointestinal disease where the lining of the bowel is broken down when exposed to gluten. The result is pain and malnutrition among other discomforts. At this point I had not realized the root cause of my problems, but as disease progressed, it was becoming glaringly obvious.

In 2008 I was finally able to go back to work when all my blood work and labs returned to normal. I was starting to feel like I was getting my life and body back when I was diagnosed with a fourth and fifth disease, the worst being myasthenia gravis. As the disease progressed, I began to lose control over my ability to chew and swallow. I was scheduled for a thymectomy in February 2010. If myasthenia gravis progresses, the lungs can become too weak to work, resulting in death by myasthenia crisis. I went through a

short remission that lasted until 2013 but spent 2014 in chemotherapy again.

I felt hopeless and feared realizing that I had no control over my own health. These Essure women found me on Facebook and asked me one question: How is your health? I was intrigued, and there began a relationship. I had been praying and hoping for remission, but now I knew there was only one way to assure the possibility of a healthy future. I needed to rid my body of Essure coils. And I spoke with all of my doctors, all of which were supportive and felt this was probably not a coincidence. Even Dr. Galen, when I tracked him down in retirement, could not argue the fact.

DR. IGLESIA: Please summarize. Thank you.

MS. AVINA: Again, I ask you to listen to this group of women who all have a story. Their lives were changed by a device that was not adequately monitored during clinical trials by physicians who were not adequately trained and by a company that has not adequately listened to their patients.

Thank you.

(Applause.)

DR. IGLESIA: Can we please play video 15? Patricia Rhodes.

(Video played.)

MS. RHODES: My name is Patricia Rhodes. I joined the STOP 2000 clinical trial at the Arizona Women's Health Research clinic in Phoenix, Arizona, because my ex forced me to get sterilized. After I joined, I was never given the opportunity I was told I would have to see the implants, to see the packaging they came in, and feel what was going to be implanted in my body. Had I been given the opportunity to feel the devices and see the

packaging, I never would have allowed them to be implanted in my body as I would have known within seconds of touching them that I was allergic to them.

In the beginning I asked at least a half a dozen times what they were made out of because I have metal allergies, before being told they were 100% surgical stainless steel with a coating to promote scar tissue growth. They made them sound so innocent and harmless. If I had known then what I learned at the end of last year, I never would have allowed them to be put in my body.

I suffered the effects of nickel allergy all over my body for 14 years, 5 months, and 2 days, until having them removed by hysterectomy in March of this year. After the procedure, I experienced pain, cramping, and bleeding. It took several months for the bleeding to stop, which they blamed on my having been on Depo-Provera, despite the fact that I had been off of it and regulated before getting the implants. If you look at my records, you'll see complaints and visits for pain and recurrent yeast and urinary tract infections I started experiencing over and over after getting Essure.

I know I'm not the only one in Phoenix who complained of the same issues. There's at least one other that I talked to in the waiting room while waiting for a follow-up appointment that had the same problems. Apparently we weren't allowed to discuss our experiences for some reason as they separated us as soon as they overheard us discussing our problems.

During the study, my paperwork was altered and/or filled out for me, instead of reflecting my true experiences. The first time I sat in the office filling out the questionnaire, I only completed part of it before the doctor took it and helped me finish it. After the first

one, I do not recall ever seeing any of the others that were filled out for me. At the end of 2008, I experienced my first pregnancy with Essure in place, because it ended in miscarriage, and they delayed getting me into the office for testing or falsified the result. They denied that I was ever pregnant, saying that there had been no pregnancies with Essure, which I since learned after finding Essure problems on Facebook last year was a lie. I had two more early term miscarriages with Essure since 2008 but didn't bother to report them to the clinic as they probably would have only denied them as well. Essure is nothing more than a torture device that causes pain, suffering, and agony for thousands of women.

The chemicals and materials in the coils cause autoimmune problems, weight gain, and very possibly cancer. They do not prevent pregnancies as much as they claimed they do. If they do not prevent pregnancy, cause thousands of women, some as young as 20, to have major surgery to try to undo the damage they've caused, what good are they doing? I've lost everything but my left ovary to Essure, and I'm still suffering from probably permanent debilitating issues they caused. Essure needs to be pulled off the market now before any more unsuspecting women end up suffering and going through needless surgeries to correct the mistake of getting them.

(Applause.)

DR. IGLESIA: Speaker No. 16. And please state your name and affiliation.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm President of the National Center for Health Research, and I'm speaking on behalf of our center and also on behalf of members of the Patient, Consumer, and Public Health Coalition. We're all nonprofit organizations, and we do not have financial ties to any product. Because I'm speaking on behalf of two groups,

I have 6 minutes, but I've only been given 3 on my thing, so please change that. I appreciate it. Thank you.

Just to give you my perspective, I'm trained in epidemiology and public health at Yale Medical School, and I've been working on issues of safety and effectiveness of medical products for, I'm sorry to say, more than 30 years.

Next, please.

Our center conducted a study of women who had problems with Essure. So this is not a random sample; it's a study of women with problems. And you can see that 86% of the women with problems reported problems with pain, mostly pelvic pain but not entirely, but generally in that area. Bleeding was reported by 34%, and this was often very excessive bleeding. Some women told us they didn't stop bleeding. Basically, they were bleeding every day of every month. Fatigue reported by 22%. And this is where we get into some autoimmune responses. Fatigue 22%, hair loss 16%, and depression, which can be autoimmune also in nature, 12%. You can see that 12% of the women had hysterectomies; 7% had allergy symptoms. And I'm not reporting the less common symptoms. Again, of the women who reported problems, these are the kinds of problems they reported, and you can see a very clear pattern that's somewhat similar to other ones, such as the ones that have been reported to the FDA directly.

Next, please.

This is a photograph of two Essure devices that had been taken out of a woman. You can see they look quite different from what they look like when they're inside. And they are in pieces as well. And some of the pieces of these devices were still in the woman who had

them taken out and still causing her pain after her Essure was removed. I think what's really important to talk about this, is that also in our study, almost -- approximately half the women -- no, I'm sorry, about a third of the women had had their Essure taken out, and about half of those women said that they had had a complete loss of all the problems they had had. So their symptoms disappeared for about half the women, and only 5% of the women said they had had no improvement after Essure was removed. So, to me, that suggests that these problems were related to their device for the vast majority of the women, even though sometimes these symptoms obviously build on each other.

Next, please.

This is from the chart that you were given by the FDA. I just looked at the most common types of pain that were reported. And there's red ink. It's a little hard to see, but I tried to show the fact that even though these numbers vary from year to year and they tend to get lower as the years go by, but if you look at the sample size and the lost to follow-up, you can see that the numbers of women correspond with the lost to follow-up. Because so many women are dropping out of the study and so many of the women dropping out are women who've had severe pain and other complications, you're losing track of them, so you can't really see them. But, even so, if you add across these pains and these are -- it was still 8% of the women at 4 years.

Next, please.

Here's another. This was Table 8 from the material you were given. And, again, looking across the pain, at total recurrent pain, it totals to 18%. Now, I assume that some of these women had pain in more than one area, so we don't know exactly how many

women based on the data that we're provided. But just to give you a sense that women are having pain in a lot of different places, and that if it does total up, it's very high, again, if you at look baseline, you look at 3 months, you look at what's happening later, the numbers of women are dropping in the study as well as the numbers reporting pain.

Next, please.

And here we combine Tables 9 and 10 to look at irregularities and bleeding, and you can see again that these numbers are quite impressive at 5 years and during that time. And, again, in talking to the women, it's clear that these are very serious problems.

Next, please.

This you've seen where things were crossed out.

Next, please.

Again, more things crossed out. So the question is, can you believe what the data are showing, or do you believe what the women are telling us? And what the women are telling us, for example, is that they were thrown out of the studies when they were having pain. When they were reporting that they wanted their Essure removed, they were thrown out of the studies, and yet it wasn't reported that they had had the pain. You've lost those women to follow-up.

Next, please.

These are the main issues for you to be considering. The safety and effectiveness compared to what? Why weren't those studies required to have a comparison group, using other kinds of birth control? A good question.

The accuracy of the data. Were the women being told to say they were satisfied

when they weren't, to say they were satisfied when they were in excruciating pain?

The next question: How do you safely remove the product? We don't know the answer to that one either.

DR. IGLESIA: Thank you.

DR. ZUCKERMAN: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 17.

DR. McDONALD-MOSLEY: Hello, my name is Dr. Raegan McDonald-Mosley. I'm here on behalf of Planned Parenthood Federation of America, and I have no financial relationship with Bayer HealthCare or conflicts of interest.

I thank the FDA staff and members of this Essure Advisory Panel for allowing me to make comments today on behalf of Planned Parenthood. We consist of a national office and 59 affiliates. Our affiliates serve more than 2.7 million patients a year. In fact, one in five American women report having received care at a Planned Parenthood health center at some point.

At Planned Parenthood, the health and safety of our patients is our top priority, and we work every day to ensure that our patients have a positive experience. With input from medical experts, we update our standards of care on a regular basis according to available medical evidence. Therefore, when Essure was approved, we recognized the potential benefits for women interested in a safe non-incisional form of permanent birth control that could be performed in an ambulatory setting without the additional risks of general anesthesia.

Planned Parenthood has always recognized the importance of a wide array of contraceptive options, and our role as a provider is to inform a woman about her options, with the inherent risks, benefits, and alternatives of each. With this information, a woman may then decide which method is best for her to accomplish her reproductive life plan and overall goal. Additionally, we recognize that many women choose permanent birth control once they've reached their desired family size.

Planned Parenthood has provided support and training for affiliates who have decided to offer this service. For the first set of affiliates that implemented Essure services, we devised a system of inter-affiliate training such that experienced Essure providers trained newer providers. And in 2011 we subsequently developed a handbook that provided clinical and operational information as well as program requirements for our affiliates.

Moreover, our affiliate risk management and quality improvement programs require affiliates to report and analyze complications related to Essure. Affiliates providing Essure have experienced low rates of accepter dissatisfaction and procedure complications; 23 affiliates provided Essure in 2013, and 24 affiliates provided this service in 2014. In this time frame, failed procedure rates reported ranged from 2.4% to 8.3% as compared to the failure rates in the pivotal clinical trial. In 2014 adverse events such as recurrent or constant pain after their procedure ranged from 1.3% to 7.1%.

Based on published literature and our experience, we continue to offer Essure as an important option. However, since many women have reported problems after Essure, we feel that further study across longer periods of time is prudent, including the establishment

and maintenance of a registry in order to determine adverse event frequencies among Essure accepters.

In summary, Planned Parenthood believes that women should have the option of undergoing an Essure procedure after adequate counseling and education about the risks and alternatives. However, we support the efforts to glean additional epidemiological information in order to further analyze the risks and side effects related to Essure.

I thank you very much for your time and consideration of our experience with Essure at Planned Parenthood.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Now, before the Panel breaks for lunch, I'd like to ask Panel members if there are any brief clarifying questions that you have for this first portion of the Open Public Hearing.

Dr. Elser.

DR. ELSER: This question is for Dr. Zuckerman. It looked like you had some categories of pain, such as dyspareunia, dysmenorrhea, and other pain, which may not be mutually exclusive. And were you adding those up across the columns?

DR. ZUCKERMAN: Yes. And that's from the chart that was in the material that FDA provided to you. So that's not the chart from our data. That's the chart from the Conceptus study. So I wasn't sure, you know -- as I said, we didn't know whether you could add them up or how much overlap there was, and I don't know the answer to that question.

DR. ELSER: Okay. So you added it up, but the chart does not add them up. So we

don't know if one patient had -- she was the one in the dysmenorrhea column and the dyspareunia column.

DR. ZUCKERMAN: That is correct. But there were other kinds of pain, I believe, that were not on that chart that were reported. So, you know, we missed those data.

DR. ELSER: Thank you.

DR. IGLESIA: Any other question?

(No response.)

DR. IGLESIA: Okay. So we will now break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room at exactly 1:30 p.m. to resume the Open Public Hearing. And I will ask that all Panel members please return at that time.

(Whereupon, at 12:43 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:44 p.m.)

DR. IGLESIA: Would everyone please take a seat so we can get started? So we will now proceed with the second portion of the Open Public Hearing. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda.

Ms. Craig will again read the Open Public Hearing disclosure process statement.

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

DR. IGLESIA: Thank you.

And we have the questions, and we'll discuss those questions during the open

forum, but at this point I'd like to call on Speaker No. 11 to go back, and if you could please introduce yourself and state your affiliation.

DR. DOURRON: Thank you, Madam Chairperson and panelists, for allowing me to present what I do. My name is Dr. N. Edward Dourron. I am a reproductive endocrinologist and robotic surgeon in Atlanta, Georgia, and I have no financial disclosures.

Next slide, please.

So my position is that I've always been out as an advocate to save patients' uteruses. I've been doing robotic myomectomies for 10 years, and that's where I preserve the uterus by removing the fibroids and allowing women to continue to have functional uteruses. So when I had patients coming to me and saying that they've only been given the alternative of a hysterectomy -- can we go to the video, please -- for removing the Essure device, it was logical for me to do what I do best, which is to work at trying to preserve the uterus.

So here I'm presenting a patient that I performed surgery on 2 -- actually, 4 weeks ago. And you can see the rigid Essure device protruding from the left fallopian tube here. With robotic surgery, you have seven points of articulation and actually four robotic arms that you can control simultaneously. What this does is it allows very precise dissection and removal of the Essure device with the uterus that's scarred around it, as well as the fallopian tube. The visualization that you have is three dimensional, high definition, magnified.

As you can see, during the sewing of the uterus, all the instruments allow precise suture placement, and with the injection of the patress (ph.), and the entire surgery can be accomplished in under 2 hours with less than 25 cc of blood loss. The advantages of robotic

surgery open -- compared to an open laparotomy procedure are that all the patients are able to go home the same day, recovery takes 2 to 3 days, the risk of infection is less, patients have one-third the blood loss, and they're able to resume normal activities much more quickly than with an open incision.

Here's the left side, and it shows the metal sticking out at the proximal portion of the tube. By looking more closely you are able to move in the camera, zoom, and actually see a small fragment of the nickel coil and remove that separately.

At the end of the surgery, the patients recover very quickly. What I do is once all the sewing is complete, I place a thin mesh over the uterus, called Interceed, that dissolves over time. But you can see how deep the suture placement can be. And I've had women that have asked to have their Essure removed in order to have additional pregnancy. So it is possible to even do a segmental resection of part of the tube and re-implant the fallopian tube so that fertility can actually be restored in patients that wish that.

It's important to remove the remaining portion of the fallopian tube because there have been reports that that could contribute to future ovarian cancer, so that it makes sense that if you're going to remove part of it, remove the entire fallopian tube. And here you can see it leaving the patient through a small belly button incision.

DR. IGLESIA: Thank you very much.

Our next presenter is -- we're going to go back to Video No. 2.

(Video played.)

DR. HUFNAGEL: In 1995, as Slide 1 shows, is that I testified against morcellation as an oncological fellow and stated that the device was defective and would spread cancer and

other diseases and it would kill women. I also discussed the problems with Ovabloc and asked for a recall many times, and that device was not recalled. It does need to be recalled.

At this time, there's a mythic concept that if we destroy the uterus or the fallopian tubes, that we're going to cause no harm, and that's literally insane thinking. These products all cause problems of fraud, battery, mayhem, and in the case of morcellation, attempted homicide and negligent homicide. Female victims are very difficult to help, but they're looking to seek healing through legal means, and they have anatomical, physiological, and psychological issues which need to be healed, and they are not getting this help. We need to look at sterilization methodology and the understanding that destructive aspects of hurting female organs is not a means of proper device creation.

All of the chemicals and cofactors made by the fallopian tube are destroyed. What do you get? Well, an example you'll get is that you'll get more rheumatoid disease in these women because you're destroying the factors made by the fallopian tube to reduce rheumatoid disease in women. Lack of ethics, lack of science, and no hormone studies. How could we create devices and not see how they affect female hormones? That is another issue of insanity in looking at this from a point of view of ethics and medical science.

I am requesting all of my documents from the FDA. I have sent a demand notice to the FBI for investigation and prosecution for all of the wrongdoings by corporations or any individuals involved. I am filing my own international legal action against these companies and against their products for mayhem and negligent homicide and other serious charges. I want to remind everyone that poor women in developing countries are used as guinea pigs.

My future work. I will be asking to work to review the MedWatch program and publicate on that. I'm here to work with everyone who wants to bring about positive change.

Thank you.

DR. IGLESIA: I'd like to invite Speaker No. 18 to come up. This speaker will have 6 minutes. Please introduce yourself and state your affiliations.

MS. FIRMALINO: I also have a PowerPoint that's supposed to automatically play for the 6 minutes.

My name is Angie Firmalino. I have no financial conflicts of interest to disclose. What you are viewing are images and posts from women suffering from Essure.

I was implanted with Essure in 2009, 3 months after the birth of my son, Elijah. I started the Essure Problems Facebook group in 2011 after finding out my coils expelled and were embedded in my uterus. After the ultrasound that revealed this, I felt very betrayed and misled, not only by my doctor but by the manufacturer. I honestly had no idea that these devices could expel from our fallopian tubes and perforate organs or embed in other areas of the body. That is just not made clear to patients at all. Even though I now know that migration and perforation are currently listed adverse events, the reality of what that means and what one faces if that happens is ruthlessly downplayed.

After creating the group to warn my female friends and family members, many women that I did not know started joining and posting similar stories of their problems with Essure. After more than 4½ years now and approaching 21,000 members in the group, I have probably read a quarter of a million posts, day after day, week after week, month after

month, posts from women in debilitating pain, women suffering, having no one who will believe them that Essure may be the cause, let alone help them. If this were men complaining of pain, bleeding, or sexual dysfunction after having a medical device implanted in their testicles, no doctor would question the cause or hesitate to remove the implant. It's just not the same for women.

I only have time to share a very small fraction of what we see in our group on a daily basis, but I will do my very best to represent these women who have put their faith in me to come here today.

The clinical trial information that Conceptus, now Bayer, presented to the FDA in 2002 is not what is happening in the real world. There is no one in this room who has more experience with what is going on in the real world with Essure problems than me and my team of administrators and the women who have lived through this nightmare. There will no doubt be women here today to tell you how happy they are with their Essure procedure. We understand and expect that. I just hope that they can understand that because of the life-altering damage this device can do to some, we believe it is not fair to sacrifice one more woman, one more mother.

Is it not advancing?

UNIDENTIFIED SPEAKER: Just say click.

MS. FIRMALINO: Click. We've watched mothers have to bury their babies after Essure coils perforated the infant's amniotic sac. We've had to mourn the loss of women in our group. We've seen suicides and we've seen death during or after Essure-related surgeries. We watch surgery after surgery every single day in our group. In fact, there's 11

surgeries going on today. The complications that come with them can be extreme. We've seen the coils in the spine, in the colon, in the kidney, in the cervix. Husbands are walking out on families because women can no longer have sex with them due to the excruciating pain. We've watched mothers cry in despair because they cannot take care of their children anymore. We watch women lose their careers, all because of problems from Essure.

There are patterns of autoimmune disease, cancer, pelvic adhesive disorder, PID, and other recurrent infections that will just not go away. These side effects are extreme. This is not just period-type cramping. The allergies some are experiencing are not just simple dermatitis. These are life-altering side effects that stop you from functioning as a person.

At the time Essure was presented to the FDA for approval in 2002, there were 281 women who had been followed for 18 months, 149 for 24 months, and 5 who had relied on Essure for 36 months. One of those five women is in our group, and so are 17 others of the clinical trial participants. They are finding us, one by one, looking for answers to their failing health and looking for help. You have heard from three of them today. At the last FDA meeting that we had regarding Essure, I invited every single person in that room to please join our group and see what is going on. Look at the reality of what is going on in the real world. No one made that effort.

Epidemico recently wrote and published a paper called "An Analysis of Adverse Event Reporting for the Essure Device in the U.S." Working with our admin team and our Facebook group, we jointly educated women on how to file an event report using the MedWatcher app. They recently presented their findings at a conference in Boston. The

Epidemico employees who had to read and enter the Essure reports told our admins they were absolutely horrified at what they were reading every day.

DR. IGLESIA: Please summarize.

MS. FIRMALINO: The fate of Essure ultimately lies in the hands of the Panel members and the FDA today. Bayer has no intention of issuing a recall or stopping any of this. It's time to take a good, hard look at this. It's time to put people before profits. Either the FDA acts in the best interest of the people or they don't. It is unlawful and inhumane to sacrifice a group of unsuspecting women for the benefit of the majority, especially over birth control.

DR. IGLESIA: Thank you very much.

MS. FIRMALINO: So my slides didn't play?

(Applause.)

DR. IGLESIA: We invite Speaker No. 19. Please state your name and affiliation.

MS. DYKEMAN: Hello, my name is Amanda Dykeman. I have been an administrator on the Essure problems page since 2012, and I have no financial conflicts to report.

Nonsurgical female sterilization, the holy grail of all birth control. For decades, researchers have tried to develop a device to occlude the fallopian tubes without surgery, but they have failed due to migration and serious side effects. In recent years there has been an increase in pressure from governments internationally to put more resources into family planning. In fact, Dr. John Kerin, a lead Australian investigator for Essure, cited this pressure in the early stages of Essure's development in a medical journal, titled "New Methods for Transcervical Cannulation of the Fallopian Tube."

"The pressure in governments and international agencies to place more resources into the population control may facilitate the accelerated development, application, and cost containment of these new devices and delivery system."

That makes it no surprise that Conceptus then appointed someone like Dr. Charles Carignan as an advisor in 1995. Dr. Carignan's work is in the introduction of new contraceptive technologies for government and international agencies such as Planned Parenthood Federation of America.

So I think it's important that someone points out the obvious. Essure was granted accelerated approval in order to provide women with low -- in the low-income population an option for permanent birth control. It was developed and intended to be pushed out in clinics, such as Planned Parenthood, to avoid unwanted pregnancies. The problem with that is that there is not enough long-term evidence to support Essure as a reliable and safe option for use, and women are becoming pregnant.

In a sworn affidavit provided to the FDA in a recent petition, clinical trial participants provided evidence of alterations made to their medical records. These alterations were made by the lead American investigator of Essure, who also held equity positions with the company, providing serious financial conflicts of interest.

When problems persist for women that have been provided free sterilization from the clinics like Planned Parenthood, they have no recourse when things go wrong. Planned Parenthood cannot assist them in emergency surgical situations, and oftentimes these women do not have insurance and cannot afford to pay out of pocket to be seen elsewhere.

Bayer can stand here today and tell you they have years of data and follow-up with

thousands of women supporting the safety and efficacy of Essure. But the truth is none of it supports Essure as safe and effective because we have seen how patients' concerns have been ignored during the clinical trials and passed off as not related to the device. The FDA must revoke Essure's PMA in order to maintain the integrity of data submitted for premarket approval.

Dr. Seifer, you asked, during the original meeting to approve Essure, what the FDA would do in 5, 10 years if we were seeing problems with Essure. Well, the fact is history has indeed been repeated with a failed nonsurgical sterilization device, and we are here to say Essure has failed, and we are all real.

DR. IGLESIA: Thank you.

I'd like to invite Speaker No. 20. And please state your name and affiliation. Thank you.

MS. MYERS: Hello, my name is Kim Myers. I am a victim of the Essure and an administrator for the Essure Problems group.

A big problem we see with Essure are all the "ifs." During the clinical trials with expert doctors and carefully screened women, they failed to place one or both devices in one out of eight women. Many women will go through this procedure, and in reality, Essure won't work for them. There are so many conditions that have to be met for Essure to work. We call them the "ifs" of Essure.

- If they can even place the devices.
- If they are properly placed.
- If they stay in place.

- If the fallopian tubes occlude.
- If you have problems finding a doctor who has enough experience to remove them, can be a problem. Then there is
- If they can even get the devices out without leaving pieces or fragments that may be hard to find and remove.

My experience with Essure included having two devices removed, two devices removed shortly after placement but then spending the next 3 years with chronic pelvic pain, which I would describe as labor-like cramps. I had several CT scans and numerous transvaginal ultrasounds, which were all deemed normal. I finally insisted on a hysterectomy.

The photo of the uterus. That's what was found, a device embedded on the outside of my uterus, during surgery. In the instructions for use manual, it states that the outer device may be visualized. This means that it often is not. This is a huge problem when the devices migrate, break, or fragment and are scattered throughout the body.

As a group, we are not anti-birth control. We are for safe, effective birth control. Essure is not safe and just has a lot of potential for things to go wrong.

I don't have enough time to express what Essure has done to me personally and what I have found it has done to other women over the years. Even if I was given more time, I don't know if I could convey the physical and emotional pain that I and other women have suffered due to these devices, the sense of utter betrayal we have felt from the medical community, who I feel has been manipulated by Bayer into placing these devices in women for profit, which has left most of us fearful for ourselves and our families' future

healthcare needs. Obviously, I feel betrayed by Bayer for putting products before patients, but one might expect that from a for-profit corporation.

But the biggest sense of betrayal is by the people who I thought were supposed to protect us and who I thought operated over and outside the money and the politics. FDA holds all the cards on our health and well-being, and I want it known how the FDA treats the consumer who they are charged with protecting. Let's remember that Essure went through the FDA's most rigorous approval process. The FDA has given Bayer an enormous amount of time over the years to present information claiming Essure is safe. The FDA gave me 3 minutes.

DR. IGLESIA: Thank you.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 21. And please state your name and affiliation.

MS. HIRMER: Hi, my name is Carrie Hirmer. I have no financial conflict of interest with Essure or Bayer. I'm an admin for the Essure Problems Facebook group and also help admin several of our subgroups.

I had Essure done in 2013. At the time, I was running my own consulting business and working on my master's degree in public policy. Within 2 weeks of Essure insertion, I developed an abscess in my left fallopian tube that resulted in a 4-day hospital stay. Two weeks later, I had a hysterectomy. My doctor told me that when he opened me up, the abscess was the size of a softball and was leaking infection into my abdomen. I have survived two brain aneurysms. They're totally unrelated to Essure. But I've survived two

brain aneurysms, and I almost died; I could have died for birth control. Due to all the problems Essure caused, the hospital stays, recovery time, I had to drop out of the graduate program I was in.

My dream had always been to get my master's degree and then go on to get my doctorate. Because of the side effects I'm left with, I am now permanently disabled. Essure took that dream from me. I went from running a successful business and being in grad school to becoming permanently disabled in less than a year.

And I'm not the only one. There are many, many more women just like me, women who lost their careers, their incomes, their financial security, their independence, their peace, their partners, their lives as they once knew it. All for birth control. There are children who no longer have the mothers they once knew. There are husbands and partners who no longer have the life partners they knew. There are families who've lost their homes, cars, farms, businesses, and so much more. All for birth control. There are women who live in constant pain, constant agony, and who will never, ever be the same. There are women who are in so much pain, they were in such despair that they took their own lives. Not one, as said earlier, but two. We have two women in our group who committed suicide. All of this for birth control.

In September of last year, I've seen a lot of women come back reporting really serious health conditions after Essure removal. We started subgroups specifically for them. That group has grown immensely and includes women with autoimmune conditions, neurological problems, spine and joint disorders, cognitive function issues, and more. We recently surveyed those women. Over 77% of them said their doctors don't know what kind

of illness or condition they have. Essure has created something in us that is outside the realm of normal diagnoses. They don't even know what to do to help us get better. Of course, had real long-term studies been done, this would have been known.

In that same survey, over 50% of them said they suffer from things like chronic fatigue, chronic headaches, overall muscle weakness, joint pain, lumbar spine pain, and have bulging discs. The women whose doctors have been able to diagnose them have been handed diagnoses like MS, myasthenia gravis, lupus, fibromyalgia, Parkinson's disease, spine and joint disorders, cognitive disorders. And the list goes on and on and on.

I won't even pretend to understand the science behind how Essure has caused all of these problems. But I do know this: When you have a group of previously healthy women with similar health conditions and one common denominator, there is definitely a problem for us; that is, Essure. We have each been given a lifelong sentence. We agreed to birth control. We did not agree to live in agony and financial ruin while the lives we once knew crumbled around us. We did not agree to watch our children live in fear of us dying. And it doesn't matter what percentage that you claim we make up of the women with Essure, because every -- no matter what the numbers say, every woman matters, every life matters --

DR. IGLESIA: Thank you.

MS. HIRMER: -- every family matters.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 22. And please state your name and

affiliation.

MS. BOGLE: My name is Cecilia Bogle, and I'm with the Essure Problems group.

Essure is supposed to be safe and effective. That has proven to be false for me and many others. Since being implanted, I've become pregnant, had multiple surgeries, and I still have fragments. I've had a hard time finding doctors that can help. In the Essure Problems group, I track and support the women who have become pregnant. These events are devastating for us as the ones who have gone through it. According to what has been reported in our group, women are miscarrying at a higher rate than average. A recent Yale study shows that chances of becoming pregnant are higher than in tubal ligation. Also the risks to the child and the mother are unknown and understudied. In our group alone, we have had 650 reported pregnancies to our group; 273 of those have been reported to miscarry. That's approximately 42%.

There have been eight babies reported to have not survived past the 24th week. Any loss of life is unacceptable. While some babies are born healthy, other babies born after Essure fails suffer from physical disabilities, underdeveloped lungs, asthma, autism, blindness, mental delays, allergies, and much more. These risks are far too high for birth control, and these need to be studied. The babies, that is.

Many families have to go through the grief and loss of a child that Essure should have prevented. After these pregnancies, these coils are left behind to continue to damage our bodies and wreak havoc. Having made the decision to not have any more children and then to find out I was pregnant and having a child was very hard for me. I was very scared, and I was very sick during that pregnancy, and I did not know what to expect. Of course,

now she is the biggest blessing ever, but there are so many things that could have gone wrong. It was a miracle for her to be as healthy as she is.

This product should've never been allowed on the market with such short-term studies for birth control that is supposed to be permanent in the human body, with such minimal study groups. The FDA needs to take action immediately to get Essure off the market, revoke the PMA, ban and prevent further harm to the public. It is unlawful and inhumane to sacrifice a group of unsuspecting women for the benefit of the majority. Our lives matter too.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 23. And please state your name and affiliation, please.

MS. ERVIN: I'm Sharilyn Ervin, part of the Essure patients. I have no affiliation with anyone.

I got my Essure on Halloween as a treat to myself. As soon as I got it, problems started happening. I had migraines, bleeding, cramping. You'd go to the ER; they would have no clue what Essure is. They have to call up somebody, they have to do this. So you're waiting and waiting. It got to the point where I lost all bowel control. My 12-year-old was my caretaker. She had no life at 12. She changed my diapers. She took me to the potty. She bathed me. She had no childhood. She would not leave my side for fear of death.

I was hospitalized for 17 weeks. No one knew what was wrong, neurologists, gynecologists, oncologists, general specialists. They were calling in people from everywhere trying to figure out what could be wrong. What is wrong is these devices that are in me,

taking away my life, taking away my kids, to be a mother to my four kids. They will never know their mother because I cannot be a mother because when I try to -- I have 10 minutes of energy, and then I'm back in the bed because of pain and the suffering. For me, it is too much.

And so all of you that have children, I would like you to think about that. You may be able to go to the park with your kids or you may be able to go to their school function. My kids, I don't even see them enough. They don't know. They think my mom is my mom. Because why? I had to move in with my mom because I lost my job. I can't qualify for anything because I don't have a diagnosis. So I have no disabilities. So at 37 I live with my mother. My four kids live with my mother. My husband lives with my mother.

How much of a burden do we have to continue to put on these women? We've been tricked. My Halloween treat for myself is no longer a treat. It's a trick, Bayer and FDA. And you need to look at this and get it off the market.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Due to the technical glitch for Speaker No. 18 with the slides, we would like you to come back up, if possible, and finish that remainder of your presentation for the slides that were not shown. So do we mind pulling those slides up? And just let us know which one you'd like to resume from because there was -- it was not scrolling during your presentation. So just let us know.

MS. FIRMALINO: Okay. I mean, you can just start it there. I only have four

paragraphs.

DR. IGLESIA: No problem.

MS. FIRMALINO: Epidemico recently wrote and published a paper, "An Analysis of Adverse Event Reporting for the Essure Device in the U.S." Working with our admin team and our Facebook group, we jointly educated women on how to file an event report using the MedWatcher app. They recently presented their findings at a conference in Boston. The Epidemico employees who had to read and enter the Essure reports told our admins that they were absolutely horrified at what they were reading every day.

You see, once you spend a few weeks or even days watching what is going on out here, you cannot help but wonder why this device is still on the market. This is not a lifesaving device. This is just birth control. There are safer and more effective options out there, like tubal ligation and vasectomy.

While we understand the desire of the Population Council and the World Health Organization and the decades of research and trials to try to find a way to sterilize women in an office setting, we are here to tell you Essure is not the answer. The fate of Essure ultimately lies in the hands of the Panel members and the FDA today. Bayer has no intention of issuing a recall or stopping any of this. They just invested millions in a new manufacturing plant in Costa Rica for Essure, and they just got approval from the FDA to replace the follow-up HSG with transvaginal ultrasound. One of the women from that clinical study just gave birth. She got pregnant after her confirmed ultrasound. And even though her clinical trial paperwork said that she would be compensated a whopping $800 if she became pregnant, she has yet to see that money.

You see, not only do we have trial participants from the original studies, we have them from a slew of postmarket studies as well. And just like in the case of Conceptus, Bayer seems to cut ties with anyone who has a problem with their device in the trial, and it's time to take a good, hard look at that. It's time to put people before profits. Either the FDA acts in the best interest of the people or they don't.

DR. IGLESIA: Thank you very much.

MS. FIRMALINO: Thank you.

(Applause.)

DR. IGLESIA: I'd like to call up Speaker No. 24. And please state your name and affiliation.

MS. GARCIA: Hello, my name is Janie Garcia, and I have no financial interest or conflict. Thank you for giving me the opportunity to come here before you and speak about the wide range of concerns and dangers regarding Essure, with emphasis on removal of these devices.

As co-administrator of two Facebook pages relating to Essure issues, I see thousands of women seeking direction and answers to their concerns. The Texas page has over 900 women, and the Essure problems multinational main page has over 21,000 members. Women who are considering Essure often join the group to ask questions, but most of the women in our group already have Essure and are seeking answers to their questions they have about the deterioration in their overall health. These women are frightened and desperate for help. On a daily basis, I see comments from thousands of women expressing a regret of having this procedure done. Women in this group consider themselves lucky to

have a removal and/or hysterectomy. Imagine looking forward to a major surgery. The fortunate women only require one surgery to remove these devices. Other women like myself have not been so lucky.

Since the manufacturer has only one protocol for removal, many doctors are removing these devices improperly, causing breakage of the device. And fragments are left behind, resulting in multiple surgeries and many other complications. This concern is the cause for one of our doctors in our group who has helped many women with removal to begin his study in hopes of developing an appropriate removal protocol. This protocol should have been in place upon approval of the device.

It would seem the women facing surgery to remove devices are a part of a separate clinical trial, one with no control or standards. My first surgery was removal of my fallopian tubes and Essure, as well as a DNC and a NovaSure ablation. I continue to have pain and excessive bleeding. So 5½ weeks later I had a hysterectomy, yet another surgery to remove my uterus, cervix, along with the fragment and clip left behind from my first surgery. Three weeks later I was fighting for my life against an infection and underwent a third surgery to drain the abscess that I had developed. And I had to wear a drain bag at home for a week to drain the abscess.

After this, for 4 months, I continued to have pain and underwent my fourth surgery to remove my left ovary, which had adhered to scar tissue throughout my pelvic area and my bowel due to the inflammatory response caused by the PET fibers found in Essure. These surgeries caused so much pain and every emotion you could possibly think of, not just for me but my entire family. This is not often acknowledged but a very real side effect.

This put the strain on relationships, finances, and quality of life.

Doctors must have a standard for removing these devices safely and completely. Had this been in place, it's likely that I would've only had one surgery. Hindsight is always 20/20. However, knowing all that I know now and have learned in this process, it seems logical to assume that the permanent sterilization being a foreign body was not a good thing or that if it did not work for someone --

DR. IGLESIA: Thank you very much. Thank you.

(Applause.)

DR. IGLESIA: Before we go on with Speaker No. 25, I'd just like to remind the audience that flash photography is not allowed.

Would Speaker No. 25 please make it up to the podium? Mr. Myers. William Myers.

(No response.)

DR. IGLESIA: Okay. How about Speaker No. 26, Mr. David Bogle.

MR. BOGLE: And I am here because my wife had got pregnant after Essure and now has fragments that are unable to be removed. And I have no financial conflict of interest.

As a husband, it is hard to see your wife in pain. I am sure that it's heart wrenching and stressful for any husband that has been put in this position. Having to watch my wife go through multiple surgeries and the risks involved, it is extremely stressful and downright scary. Our wives that have been victims of this dangerous device are not the only victims. Watching my wife in pain and unable to do the things she used to be able to do has taken a toll on my entire family. There are children with injured mothers and husbands that have to cope with the complications from Essure. The stress upon our relationship and intimacy,

though not talked about a lot, is a big factor when this implant fails our wives due to where Essure is located. I can live with the failure to prevent pregnancy, and I love our daughter regardless, but the failure to be safe in the human body is unacceptable.

I believe action needs to be taken to assure these injuries do not get ignored or continue to happen to unsuspecting women everywhere. More studies are not going to make this product any safer. I believe what is happening right now with women that already have this device speaks for itself. I feel a vasectomy or a tubal ligation is already safer and more effective than Essure. There is no need for this product to be put in another woman's body.

Thank you.

(Applause.)

DR. IGLESIA: Thank you very much.

Speaker No. 27. Please state your name and affiliation.

MR. SHIELDS: Good afternoon. My name is Wayne Shields. I'm President and CEO of the Association of Reproductive Health Professionals. I haven't received any financial support to be here today, and I'm here to represent my organization's 14,000 healthcare provider members, who are physicians and nurse practitioners, physician assistants, nurse midwives, and counselors. ARHP has in the past received grant support from Bayer.

I wanted to thank the Panel today for basically how well you handle these types of inquiries, and ARHP's members and leaders really respect the thoughtful process that you take and appreciate your continued reliance on the best available science to inform your decision making. But I also want to, on behalf of my organization, respect and acknowledge

the experiences of the women you've heard in this room today. They're very real, and it's important that we hear them and important that the providers hear them as well, my people.

ARHP believes that more comprehensive provider education is part of the solution, and we do believe and support continued availability of transcervical sterilization, like Essure. We just advocate for more effective, comprehensive provider education as part of the solution.

To describe the people I work with, they're actually a lot like you on the Panel. A lot of folks are researchers, health researchers and professionals who also practice healthcare, and that's who my folks are. But we're an accredited group who focuses on sexual and reproductive health specifically. So this is an issue that's key to my folks. And really they do need to be -- do the best possible evidence-based, patient-centered care when it comes to this method and any contraceptive method. So as I said, we advocate for that as a solution.

ARHP really supports evidence-based education and policy as well, and we look to the literature and expert consensus to guide provider education. When the literature isn't full enough, we rely on guidance from other groups, like ACOG, and we rely on consensus of experts in order to develop our education. And we have a huge emphasis on what's called client-centered care. That is kind of a fancy way of saying it's not up to the healthcare provider to make decisions for every individual. It's up to that individual, especially because everybody's unique. So we really want the availability of as many safe and effective choices as possible. The alternative to a pregnancy that's not prevented is there are issues,

including -- up to and including continuing with a pregnancy that has many health risks. So we can't avoid that as part of the conversation either.

We do take the position that transcervical sterilization is an important option to women, especially for those who no longer want children but prefer to avoid the more invasive process of tubal ligation or the health risks of pregnancy.

As an organization, we spend a lot of time and energy at educating providers about options counseling and in particular about educating about risk and benefits.

DR. IGLESIA: Thank you very much.

MR. SHIELDS: Thank you.

DR. IGLESIA: Thank you.

I'd like to invite Speaker No. 28 to come up. And please introduce yourself and state your affiliation.

DR. NOVOA: Hello, my name is Dr. Julio Novoa. I am a practicing OB/GYN from El Paso, Texas. I've been in private practice since 1999 and have managed over 15,000 patient cases, including 5,000 deliveries, and have performed over 1,000 in-office, awake surgical procedures and over 1,000 laparoscopic tubal ligations. I am the main commentator for the Essure Problems forum on Facebook, representing over 20,000 women from the United States, Canada, the U.K., Ireland, Australia, the Netherlands, Spain, Finland, and New Zealand. I would like to say, for the record, that I have no conflicts of interests to declare, and I am not being paid by anyone to be here, or any organization for my testimony.

Essure problems patient surveys and Essure MAUDE data analysis have shown exceptionally high complication numbers, including pelvic pain, abnormal bleeding,

improper placement, implant migration, and device failure leading to pregnancy. These percentages represent thousands of real people and are in stark contrast to what is quoted in the company-sponsored trials. The FDA's reliance on company-sponsored clinical data is by its very nature flawed. Published data suggesting a high level of efficiency and safety regarding the Essure is based on experienced clinicians representing ideal and not real-case scenarios. Relying so heavily on such small group sampling factors out time and procedural errors, learning curve errors, and malpractice errors caused by the novice hysteroscopic surgeon or, most commonly, the inadequately trained and inexperienced gynecologist placing the Essures.

The Essure MAUDE data is also limited. It does not include the 16,000 adverse reports file turned over to the FDA by Bayer. And more importantly, the vast majority of patients are completely unaware that the MAUDE data reporting system even exists. Therefore, the actual number of adverse reports appears to be grossly underreported and well above 25,000 adverse cases. Data collection from Essure problem surveys lists over 500 unintended pregnancies with ectopic pregnancies, and Essure-induced abortion rates as high as 40%. Further, Essure-related salpingostomies, salpingectomies, and/or hysterectomies now average over 100 cases per month, with 11 cases being done just today.

The FDA is also guilty of complacency by continuing to allow Bayer to advertise the placement of the Essure as a nonsurgical procedure, which this is on the website, in the literature, and in the clinical manual as nonsurgical. The placement of the Essure is absolutely and unequivocally a surgical procedure. Medical state board regulations,

hospitals, surgical privileges, CPT coding, as well as insurance company preauthorizations list the Essure operative hysteroscopic procedure as a surgical procedure. Advertising the Essure as nonsurgical is not only misleading but unethical and potentially criminally deceptive. Allowing this to continue compromises the trust and welfare of the U.S. consumer and must stop immediately. Before the close of this meeting, the FDA should order Bayer to stop advertising the Essure as nonsurgical. They'd do anything less --

DR. IGLESIA: Thank you very much. Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 29. And please do state your name and affiliation.

DR. MONTEITH: I was told I had 6 minutes, so I'm not sure --

DR. IGLESIA: You do indeed, sir.

DR. MONTEITH: Okay. My name is Dr. Charles Monteith, and the only conflict of interest I have is with myself, because I am here to speak out against the Essure device, but I also make my living based on treating Essure-related complications.

As a former medical director of Planned Parenthood of Central North Carolina, over a 4-year period I did over 60 Essure insertion procedures. Currently I practice -- my practice is devoted to female sterilization reversal, and I have performed, over the last 6 years, 233 surgeries to remove Essure devices, both for women who wish to become pregnant and for women who are having side effects from the device.

Sterilization procedures should be as safe to use as fire extinguishers. They should be easy to use, highly reliable, and should not cause harm to the user. I would like the Panel to consider a fire extinguisher that my company has designed. We have found that, in

our pivotal trial, it discharges propellant 88% of the time with the first time used. If it doesn't work the first time, that's okay. You turn it upside down, you shake it, you wait 10 minutes, and an additional 4% of the time it will work. We feel that this is acceptable because it will put those fires out. Only 8% of the time did the extinguisher not work, and in this case we recommend a more traditional, older method like running and calling 911. We had four adverse events. The extinguisher exploded and embedded propellant into the hand of the user, but that was corrected with surgical debridement. My question is, would any of us approve this fire extinguisher for general public use? Would any of us feel comfortable with this less than perfect fire extinguisher in our home?

One of the biggest problems I had with inserting Essure is that I never knew if it was going to work when I sat down to insert it. I was never sure if I was going to be able to get the device in bilaterally. And if I did, I was never sure if I was going to see the patient back for the confirmation test. In the pivotal trial, basically about 1 out 10 times you couldn't insert it successfully the first time. So if I asked everyone to fly on an airplane with me and the landing gear would not retract 1 out of 10 times, how many of you would want to fly with me? It's okay, we can take the plane back around again and try a second time, and a lot of the times it will work the second time. But if not, we can abort and just do a soft water landing. Essentially, that's what we're dealing with when we're talking about Essure sterilization. When you're going into a sterilization procedure, you may only have one time to get it right.

In regards to Essure complications, unlike hormonal treatment, Essure can't just be stopped. Unlike intrauterine contraception, there's just no string to pull on to remove the

device. Essure can only be removed with surgery under general anesthesia. The recommended treatment has been cornual resection, although most gynecologic surgeons have limited experience with cornual resection. Attempting to remove the device with traction can oftentimes result in fracture of the device. Women who have Essure complications are having hysterectomy procedures because this is a surgical procedure that most gynecological surgeons are familiar with.

We have just conducted a 14-year, non-randomized, uncontrolled trial on the effects of Essure on American women, the complications of which have been reported by self-reporting, which we know notoriously underestimates complications. The complications have come from small trials and some international trials. Guys, we know where we are with this. We have reached this fork in the road. And as the late Yogi Berra said, when you get to the fork in the road, you got to take it. It is time for a randomized controlled trial on Essure versus other methods of sterilization.

I would like to challenge Bayer that if you truly care about the health of American women, that you would fund such a study and have this study look at patient-centered outcomes, and have a third party who's not affiliated monitor and oversee this study. I would like to commend Bayer on improving the physician educational materials. Those materials were far better than anything I ever had when I was with Conceptus, when I inserted the device and Conceptus was the manufacturer. But you can also look at the device and see how -- or that educational handout and see how difficult it is. It's not always an easy procedure to do.

In conclusion, sterilization procedures should have the same safety standards as do

fire extinguishers. A fire extinguisher that requires many steps, does not work 12% of the time, harms its users, requires major surgical treatment for those injured by the device would not be considered acceptable for public safety. I don't see why we would consider the Essure sterilization method any differently.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 30 to the podium. Let's make way. Please state your name and affiliation.

DR. NOORCHASHM: Good afternoon. My name is Hooman Noorchashm. I am a surgeon and a Ph.D. immunologist in Philadelphia.

I've had the very unfortunate privilege of being in this very room before a similar panel advocating for patient safety, for women's health, for medical ethics. And I have to tell you that without a clear understanding of medical ethical principles, which there's very scarce discussion of here, practice will be turning into unforgivable harm. And first I want to remind every federal agent and federal officer here that you are guardians of the public and of an agency that's charged with protecting every American life. You're not here to protect Bayer's interests or the gynecological community's interests. You are here to protect the interests of people, of the public.

It's very ironic to me that we're sitting back here, the advocates and the patients, and Bayer is sitting on that side with FDA and with the expert Panel. Very ironic and surprising.

Ladies and gentlemen, you've heard a lot about Essure. It's a nickel-based coil. It's

placed in the fallopian tubes in otherwise young and healthy women. Okay. This device is not designed to cure an incurable disease. It's designed to irreversibly prevent pregnancy, and there is a lot of doubt as to whether or not it's effective here, okay? It's designed to create an inflammatory response in the mucosal surface, which is poorly understood and really was not part of the PMA process, the study of basic immunology. I think if you tapped Dr. Milner's expertise here, you'll find out that the study of the mucosal immune response to nickel was never part of the original PMA process. This inflammatory process goes rogue, and what you're seeing here is a group of women -- and I'm going to ask you folks to stand up and remain standing until I'm done so everyone sees you clearly.

So it appears that Bayer here and the gynecological industry are having us accept this concept that majority benefit justifies avoidable harm to minority subsets of people. And, you know, I ask you to consider what failed societies of the past have done that. You know, we're talking about something that's avoidable. It's a medical device that's completely avoidable. And what I want to know from this Panel is what percent harm are you going to accept, 0.1%, 1%, 5%, 10%? And how are you going to justify that? Preventable, avoidable device, avoidable harm, this minority subset of women.

You know, we're at a crossroad here in American medicine and in particular, it appears, in women's health and at the Center for Devices and Radiological Health, okay, because it appears that the preservation of choice, the preservation of convenience, the preservation of majority benefit are overriding the sound principles of medical ethics, okay? And that's okay as long as it's a minority subset of lives. I ask you, is that acceptable? I ask industry, is that acceptable? I ask the expert Panel, is that acceptable? I ask the FDA, is

that acceptable?

You see these folks who are standing up here? They can't even take their case to court because the Supreme Court of the United States has taken away their right to seek justice in the court system --

DR. IGLESIA: Thank you.

DR. NOORCHASHM: -- because this device is a PMA-approved device.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 31 to the podium. And please state your name and affiliation as well.

DR. REED: My name is Amy Reed. I don't have anything to claim. I have my M.D. and Ph.D. in immunology, and I'm here to support all of these women who have been harmed by these Essure coils. And I'm here to talk to you about why it might be easy and convenient to do it in an office or an outpatient setting, and it might have great efficacy or maybe not. But the fundamental basis for the Essure coil is immunologically flawed, as any immunologist would say and my husband referred to.

How Essure coils work. The basis for which they work and the problems that they cause and the inability to quickly fix them, that makes them an unsafe device. And I'm sorry if this wasn't studied appropriately, and that's what I'm hearing beforehand. The Essure coils, the nickel, and then the metal, and then they cause scarring. And I've heard that some people dumb this down and say, oh, well, we use similar metal in stents. But that's not a mucosal surface. That's like someone saying I need contact solution, and I say, oh, I

have some nail polish remover. It's safe. It's apples and oranges; it's wrong marketing, and it's lying to an entire group of women.

Regardless, this inflammation goes completely out of whack, as you have here. Women are presenting just like you would see in a rheumatologist's office, hair loss, rashes, joint pain, tired, all of these diffused kind of, well, we really can't pin it down and it doesn't happen all the time. These are classic symptoms of immune symptoms run awry. And these poor, otherwise healthy women are subjected to these horrific, big abdominal repeated operations to try and fix this. But you can't stop this runaway train. In a lot of cases, you can't reverse an immune system that's gone crazy just by an operation. And I'm sure these women, too, have experience with this.

So what recourse do these women have that have been subject to this deliberate inflammation? And like my husband alluded to, it's because you all put this stamp of approval on it. The Supreme Court said the PMA process says this is a perfect device. You don't have recourse to seek out damages in a civil court. Sorry, the FDA says it works and the federal government says it works. But, importantly, what kind of onus of responsibility does that put back onto the company if they have 0% liability exposure? A bunch of women with a few symptoms comes to them. The federal government says they're protected. None. They have no incentive to seek out what's going on here.

So I ask you, the members of the Panel, the FDA, we don't need registries, we don't need to hurt any more women. There are plenty of them here.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Speaker No. 32. Speaker No. 32. And just please state your name and affiliation.

MR. ROKICKI: My name is Ryszard Rokicki. I'm independent researcher in metal finishing field, specializing in biochemical compatibility improvement of medical device made of nitinol, stainless steel, and cobalt formulary. My credentials can be found from ResearchGate webpage. I report no conflict of interest.

After denied my citizen petition and restricted from public view my open letter to FDA Commissioner and most recently my comments concerning safety of Essure, FDA should be well aware what's causing the Essure-made problems and how to fix it.

In my opinion, there are only two ways to resolve the sometimes severe medical problems connected to Essure: totally ban it or make it safe. To make it safe, the faulty nitinol material outer coil of device with surface intermetallic inclusions should be detected and discarded before device is assembled. The only way to achieve this is to use very simple, cheap, 100% reliable chemical test for detection of nitinol surface intermetallic inclusions.

The uniform nickel leaching from properly finished nitinol without surface intermetallic inclusions, even if galvanically coupled to another metal, as in case of Essure, is of negligible importance. However, nitinol surface inclusions of adjusted matrices are source of catastrophic nickel leaching to surrounding tissue after implantation.

Somebody can ask, why don't we hear a similar complaint of people implanted with other kinds of nitinol medical device such as stent, heart valves? The answer is place of

implantation. Stents, heart valves are vascular devices permanently exposed to blood flow, and therefore nickel leached from them to surrounding blood is carried away and eventually leaves human organism with urine. However, we have totally different situation with Essure, which is permanently embedded in tissue of fallopian tube. In this case, leached nickel from surface inclusion or adjacent matrix stay and accumulate in tissue which is in direct contact with leakage.

At present, checking nitinol medical device for surface intermetallic inclusion is governed by ASTM F206 test, which is performed visually by inspecting nitinol samples. This test was the reason given by FDA for denying my citizen petition, which demanded the introduction of more reliable, 100% pure sodium hypochlorite test procedure. The FDA stated that visually inspected samples of nitinol lots per present test will protect public health while not overburdening manufacturer of nitinol. This is an important statement. However --

DR. IGLESIA: Can you please summarize?

MR. ROKICKI: Yes, thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Our next speaker is Speaker No. 33. And this speaker will have 9 minutes.

MR. BELL: Good afternoon. I'm Mark Bell. I am a licensed registered metallurgical engineer, and I wanted to talk about the Essure failures. I don't have an interest in Bayer. As a consultant, people hire me to give an unbiased, factual engineering opinion. And so

that's what this presentation is going to be. So it's just the facts. I try not to be an advocate, but as an engineer, I can present the facts. But it's hard, it's difficult not to get emotionally involved because I've got daughters-in-laws, I've got a wife, I've got nieces, and this really speaks to -- everybody can identify or empathize with this problem.

So my analysis. I think that just the physical way the Essure is being made is -- the ones that I've seen, there's latent manufacturing processing defects. These didn't come from being in situ in service inside the ladies. It's actually preexisting, so I call it latent.

Next, please.

I've introduced myself. I have 40 years of experience. I do failure analysis. I've done probably 1,000 of them. Different types of machinery, different types of metals. Some pharmaceutical, some biomedical, but a lot of it is food processing, oil, energy, and just metals.

It's my expert opinion, based on the studies I've done, is that Essure is not a safe product, especially compared to what I've seen industry be willing to scrap, walk away from if it's a defective material, not to continue to process it, not to put money into it, not to sell it, and not to have it in the field. And once they find out there's something wrong with it, my experience with industry is they pull it. It's good business, it's moral, and it's a good engineering decision not to let it stay in service.

Mid-level engineers have the power, if they see something defective in a Fortune 500 company -- if I've seen something wrong with a big expensive compressor, I write a stop order. Manufacturing stops until the problem gets addressed. And that's the same way I have done my analysis with Essure, is to evaluate this on a factual engineering decision.

So next, please. Please.

We talk about risk analysis. I'm sure most of you all have seen charts like this. The idea is you've got severity, and you've got likelihood. What you want to do is avoid the scenarios where you get a high likelihood and a high severity. In that red up there, that's unacceptable. You want to avoid situations like that.

Next slide.

Terrible. Sorry about the lighting. It repeats what I just said, avoid combinations of high severity and high likelihood. And what I've seen on Essure manufacturing, you've got a high likelihood of a failure. And the rest of the day has been spent on how severe it is when these things do fail.

Next slide.

So here's an Essure that I've looked at in my lab.

Next slide.

I can tell when -- this is a stainless steel wire from Essure. Now, this is the end that's probably been cut from manufacturing. It's fine, but the point I show you is, is you can distinguish between something that's failed in service and something that is cut. This probably is acceptable.

Go ahead.

See, it's just a close-up. That's a very thin stainless steel wire that's been cut.

Go ahead.

That's the marker that shows you how far you should pull the Essure out. It's stainless steel, but you can see how it's expanded. You can see the desiccated body tissues

on it. It's a good way to analyze these products.

Next slide.

See the ribbon? There's a blue arrow on there.

Let's go to the next slide.

That blue arrow pointed to the tip of this ribbon. Now, this ribbon is probably three-tenths of a millimeter wide, and it's very thin, and I have no idea what the loading is on a human body in the fallopian tubes, but apparently it migrates, it moves. There are stresses on it. And let's look at some of the flaws in the metal that might accentuate the loading of the body stresses.

Next slide.

And these are latent material defects, is what we're talking about. They existed before it was even inserted.

Next slide. Boy, if those overhead lights could be dimmed. This is a good slide. It's from an electron microscope. Is anybody going to do that? Dim the overhead lights because that slide is washed out. If you could, please.

What this is showing is probably some cracks in the edge of that ribbon. How do you make a part like that? You can't machine it; you can't grind it. You have to be very careful as you draw it and bring it through the tooling. I think there are some cracks on this, and these cracks are parallel with the edge of the ribbon.

Next slide, please.

This is the same thing. There's an edge. There are some cracks in there, or there are some surface defects, and as the ribbon is bent and flexes, these defects will act as stress

concentrations and make it very likely that the ribbon will fail and break in service.

Next slide, please. Go ahead, next slide. Yeah. Next slide.

See, I've got some arrows pointing to where these surface defects are. Are they cracked? They could be. We need to do some more analysis, but I think it's good calling it a defect, and this could initiate the fracture of the ribbon.

Next slide, please.

This is just the surface finish. It's not polished; it's just rolled. And this is the nickel-titanium ribbon alloy. Fairly rough. I would be very surprised if that's acceptable to be in a medical implant. Usually I see things that are electropolished and very, very clean surfaces.

Next slide, please.

So I would consider even this to be a latent defect. And you can see the horizontal lines from the rolling and the handling of the ribbon.

Next slide, please.

Some things you can just look at. The tip of the insert, do you see where the red arrow is?

Next slide.

That's that melted tip of stainless steel, and even that gets damaged from packaging, from handling, or from removal.

Next slide, please.

Just a close-up of that. That's not a defect. That's probably not going to cause a failure, but it's easy to find things like that.

Next slide, please.

These are the stainless steel wires. Very clean, very good. They're not nickel-titanium.

Next slide.

The edge. The crimped nickel-titanium is that sheet that's crimped over the wire. I think it might have failed there.

DR. IGLESIA: Please summarize.

MR. BELL: Next slide, please.

My recommendation is that a stop order -- these Essure products should be stopped from being put on the market until more work has been done to show that there are preexisting latent defects.

DR. IGLESIA: Thank you very much.

MR. BELL: Thank you.

(Applause.)

DR. IGLESIA: Speaker No. 34. And please introduce yourself and state your affiliation.

MS. SHEPPARD: My name is Audrey Sheppard. I have no financial relationship with any organization affected by the topic of this meeting. Professionally, I consult to organizations seeking to see that safe, effective products are available to fulfill women's unmet needs.

In late 1994, I joined FDA's new Office of Women's Health. As a layperson, neither a scientist nor a health practitioner, during my 5-year stint at the office, 4 years as its director, my emphasis was making sure that science was faithfully followed and also taking

a pro-consumer approach to women's health questions and issues. I have the highest regard for women consumers as they champion their own health needs and consult their healthcare providers about what makes the most sense for them. And I take most seriously the testimony of the patients sitting around me that we're hearing from today.

My now 25-year history in women's health led me to my decision to speak today because I think that your review is critically important. With a one-of-a-kind product in the category of permanent contraception, there may be a strong need for action to further protect the future female consumer. But what are those actions? I've rewritten this a lot.

We all know that women, nationwide, use and depend on various FDA-approved methods. Ninety-nine percent of American women ages 15 to 44 have used at least one contraceptive method during their lives, and permanent birth control is the second-most common form of contraception employed by American women. Like any product the FDA approves, this one must pass scientific hurdles and continue to pass them. We can only imagine that there are tens of thousands of women who have the product who are doing well, appreciate the benefit of not having to have surgery, to take hormones, who are going about their lives today. As advisors to this Panel, you have your work cut out for you because weighing the need versus the problems is really, really tough.

I can't necessarily follow all of this. Okay, I am optimistic that patients, advocates, clinicians, the company, with a careful review of all available data, that you, the advisors, and you, the FDA and the division, will find the right answer. This is not an easy one, and I don't envy you.

Thank you for your time.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I invite Speaker No. 35 to the microphone. And please state your name and your affiliation.

DR. JURAN: I have slides, too. My slides?

DR. IGLESIA: Got those slides up? Do we want to work on that and go to Speaker No. 36? Let's do that. I apologize. If you would just work with the people on the side and we'll move to Speaker No. 36.

MS. HENZE RUSSELL: I have slides.

(Laughter.)

DR. IGLESIA: And we have them. Please state your name and your affiliation.

MS. HENZE RUSSELL: Thank you. I am Laura Henze Russell, the principal of Precision Research and Communications. I have no conflicts to disclose. I'm here to present and call for a framework for precision devices to look at whether a device such as Essure is right for you, for the individual patient.

Next slide, please.

So patients are on a bell curve. The lucky ones that are not in this room are in the fat and happy parts of the bell curve. The people who are here and the 20,000 that they represent are on the tail ends of the bell curve, what I call the bell curse. So 1% to 3% we currently have identified as being in the bell curse. Unfortunately, it tends to grow over time. Here's an early warning signal. A number of women are losing fillings and teeth at early ages, which shows the impact of bioaccumulation for people with genetic methylation

defects when there's the synergistic impacts of metals, perhaps in your fillings, of galvanism, and so forth.

Next slide, please. Next slide.

This slide presents 12 gene variants that are associated with methylation defects that have been identified with heavy metals toxicity. The primary route for nickel toxicity is depletion of glutathione. That's essential for many processes in the body, and as we've heard, inflammation is the root of many chronic disease processes.

Next slide, please.

OB/GYNs help women bear and then care for children, the next generation of Americans. We ask you, throughout the process from approval to postmarket surveillance, to use the highest standards for safety.

Clinical trials need larger numbers, longer duration, basket studies. There are pretests that can be done to determine blood reactivity to device materials that can be used in advance, in addition to patch tests for allergies. You've heard, though, it's not just about allergies; it's immune reactivity. So we should screen patients for exclusion factors based on them. We need informed consent for health and cost impacts. The cost impacts are off the charts. Postmarket surveillance. And I would like to see all panels have a toxicologist and a geneticist on them.

Next slide, please. Next slide.

The outcomes will be better health and lower healthcare costs for all stakeholders. It will help women's lives and reduce ugly surprises.

The last slide, please.

In conclusion, Essure is easy in, high risk for too many, and hard and costly to remove. It should not be used. It should be recalled. There are lower-risk, safer alternatives. We ask you to join a call for medical and dental device safety urgent reform. If you have any questions, please contact me or other women in this room.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Okay, we're going to still move on to Speaker No. 37, please. And please state your name and affiliation.

MS. PEARSON: Hi, I'm Cindy Pearson. I'm the Executive Director of the National Women's Health Network. We don't accept any financial support from pharmaceutical companies or medical device manufacturers.

In 2002 we spoke before this Committee advocating for the approval of Essure. At that time we commented on the importance of providing information on the risks, benefits, and potential consequences of Essure to prospective users. In light of recent developments and the new evidence brought forth in the form of women's personal accounts, the network now believes that the FDA should require Bayer to significantly revise the patient information guide and to sponsor a national registry. These steps, which are within the authority of the FDA, would go a long way towards meeting women's needs for full, accurate, and objective information about Essure.

The personal and brave testimony of the women speaking here today should not be dismissed by the Panel simply because it did not result from a clinical trial. Women's

reports of pelvic pain and autoimmune disorders should be taken seriously, and these experiences should be easily available to other women considering Essure. Women who are considering using this device deserve to know this information. No woman should learn after the fact that more information was available which could have affected her decision to take a particular drug or use a certain medical device.

So today we ask the Panel to recommend that the FDA change the labeling and patient information guide for Essure. A paragraph should be added explaining that women have experienced an array of adverse health effects after receiving Essure, and this section should explain that while these effects were not reported during the clinical trials or not reported in significant numbers, the information is being added in order to be transparent about women's experiences with this product.

We also ask the Panel to recommend that the FDA take patient labeling one step further and require that women receive written information about the device prior to implantation. The FDA should use all of its resources to make this knowledge sharing of women's experiences real.

And, finally, today we call for the creation of a national registry to serve as a central database for women who have received Essure. This registry should be funded by Bayer and administered by a third-party vendor. The purpose would be to make sure that all women with Essure are followed and that data collection and analysis is not controlled by the Sponsor. Requiring a registry is within the authority of the FDA, and we urge the Panel to recommend this important step.

Ignoring the voices of women standing before you today leaves out women's

experiences that do not fit the narrative that serves the purposes of the Sponsor. The physical and emotional effects these women have suffered are real. Their stories and voices deserve to be heard and respected.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: We're ready for Speaker No. 35. Thank you for your patience. And when you come up to the microphone, just state your name and your affiliation.

DR. JURAN: My name is Rupal Juran, and I am a board certified OB/GYN. I'm also fellowship trained in minimally invasive GYN surgery.

Next slide, please.

I have no financial disclosures, and I have no financial relationship with Bayer.

Next slide.

As a gynecologist, I talk to women about health issues every day, and I feel that symptoms reported as being related to Essure unfortunately affect the entire population of women at pretty high rates, as this slide shows. And I wanted to demonstrate with this slide the frequency of many of these health issues that women and I, myself, as a woman, have faced throughout our lives. As a gynecologist, I've seen these issues in women who have gotten tubals, whose partners have gotten vasectomies, and who are using no birth control at all. I also want to point out, the lifetime hysterectomy rate among American women is 45%, and these numbers are all from peer-reviewed papers published in scientific journals.

Next slide, please.

This slide demonstrates the lifetime prevalence of other medical issues that we, as women, may face throughout our lives. Unfortunately, many of these are pretty common too.

Next slide, please.

All that being said, first, I want to say that the medical and health issues faced by all the women who came here today are very real. And, you know, if a patient came to me saying she wasn't comfortable with her coils and she really wanted to get them out, I would say this is your body, let's get them out. But I am concerned that women in a vulnerable position, who already are not feeling well, are being told they must have more surgery or being told that simply removing their Essure coils is going to resolve their health issues, or being told that they need to have a hysterectomy to remove the coils, which may not be true. The health issues that women face after Essure may or may not be related to their devices, but I'm concerned that women are being told that they need to have more surgery to cure them.

Next slide, please.

On a different tack, when a patient requests sterilization for herself, we have two options. And this has been discussed already, but one option is tubal ligation, which does require general anesthesia and abdominal incisions, and the failure rate can be as high as 3%, and the complications can include perforation of bowel, bladder, or uterus at a rate of 0.4% to 1%, and 4 in 100,000 result in death. And I'm sad to say that I've seen some of these complications after tubals.

Next slide, please.

By contrast, the only other option for female sterilization is Essure, with the nickel-titanium coils placed in fallopian tubes usually without having to access the abdomen. The risks of perforation and expulsion are part of the counseling, as seen here on this slide. And then the risk of hysteroscopy include the small risk of perforation and hemorrhage.

Next slide, please.

So I want to point out that I feel that Essure should remain an option for women. And while no method is 100% effective or 100% complication free -- and complications from all sterilization types are rare. But, overall, the complications from Essure do tend to be minor compared to the complications that we see after tubals, and Essure has been shown to be more effective. And I am looking forward to more data in that regard as well.

And the next slide shows my references. I also want to, on a personal note, say that in our practice we've done over 1,300 Essures, and I personally have done about 200, and I feel very -- I'm so glad that my patients could have that experience. We have no pregnancies. We have no damage to bowel, bladder, or vasculature with our Essure procedures. We have a very high patient -- rate of patient satisfaction. I'm very glad we were able --

DR. IGLESIA: Thank you.

DR. JURAN: -- to offer that to our patients instead of abdominal surgery.

DR. IGLESIA: Thank you very much.

I'd like to invite Speaker No. 38. Speaker No. 38. And when you make your way up to the microphone, then just please state your name and affiliation.

MS. ROMERO: Good afternoon. My name is Tabatha Romero, and I have no affiliation with Bayer.

On June 4th, 2012, I was implanted -- oh, I'm sorry. Excuse me, I have some slides. And where is the little monitor that I can -- oh, okay. Perfect.

DR. IGLESIA: Do we have her slides before I start the timer? Is that it?

MS. ROMERO: That is it.

DR. IGLESIA: Great.

MS. ROMERO: Okay. On June 4th, 2012, I was implanted with two different versions of the Essure device, ESS305 and ESS305-R1.

You can switch the slide.

It has been the worst mistake of my life. I currently suffer from 18 side effects since implantation. The most noticeable and life-altering side effects are severe daily pain, extreme fatigue, noticeable hair loss, severe cramping and debilitating menses, continual yeast infection, brain fog, painful intercourse, and depression. After 2 years of receiving zero help from my physicians with my pain, dissatisfaction of comfortability with the implants, and many other symptoms, I went out in search of what could be done to remove Essure.

I got a hold of my implanting report, HSG images -- you may click the slide -- and radiology report. It was then that I discovered -- the next one -- several discrepancies in the operative report -- the next one -- and radiology reporting, and an even greater finding. Both right and left coils were positioned incorrectly, in which you consider a grade 3 position, too distal into the fallopian tubes.

In months to follow -- next slides -- I would encounter woman after woman joining the group who were also suffering from incorrectly placed devices, all the while being told by their physicians that everything was normal or that we were the very rare cases of Essure. But not so fast. Because your Panel was fully aware of many flaws, one that I would like to bring the attention to is the failure rate of 12% in the clinical trials. And that failure rate was among expert hysteroscopists. In fact, your Panel spoke in great detail that the probability of the failure rate of 12% would increase when introduced to practicing 35,000 GYNs who are not experts.

Dr. Noller, who was on the Panel, basically screamed from the rooftops about the failure rate, and I quote him in regards to the failure rate. "I expect it's going to be 20% among people who don't do this very often. So even with the 12% rate, if women are told up front, unless there is a fallback plan like laparoscopy at the same time, I don't know why they would accept this." He went on to add, "It just doesn't say now that there is a one in eight chance that this won't work. And I think every women deserves to be told up front, in big letters in a box, you know, this isn't perfect."

Your Panel knew and acknowledged this device wasn't perfect. Yet, you approved it with a preemption status as though it were, and that is criminal. I want to know why physicians who implant Essure are not trained to remove it. The product labeling clearly states that we can demand it be removed. However, implanting physicians claim it cannot be done or that it can only be done by hysterectomy. I did not sign up at the age of 33, now 36, to have my female reproductive organs removed. A hysterectomy is unacceptable to me and my family. My wishes about what happens to my body deserves to be respected. I

am a wife, a mother, daughter, sister, aunt, friend, and business professional who just wants her life back.

DR. IGLESIA: Thank you.

MS. ROMERO: This product has altered my life and has killed my spirit, and it needs to be recalled.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I invite Speaker No. 39 to the microphone. And please state your name as well as your affiliation.

MS. RUSMISELL: Before I start, we're going to -- she's going to stand over there and click my slides for me because the technology is not --

DR. IGLESIA: No problem.

MS. RUSMISELL: -- provided the same for the public as it was the FDA and Bayer.

DR. IGLESIA: Do we have her slides? Okay, I'm going to ask you to come over to the side and just check on your slides for a second, and we'll come right back to you.

We invite Speaker No. 40 to the microphone.

MS. CERVANTES: I have slides also.

DR. IGLESIA: And let's check on her slides as well. And we do not have your slides. Okay, would you like to step to the side as well?

Speaker No. 41. And please state your name and affiliation. Thank you for your patience.

MS. HOLT: My name is Amanda Holt, and I have no financial affiliations to disclose.

I am a wife to Chris, I am a mother to Carter, Cameron, and Cailyn, and I'm also an Essure victim. I'll begin by saying that I don't believe that the FDA will force Bayer to recall Essure. Unfortunately 20,000 similar voices will simply never be statistically relevant enough. I'm here to beg for information, data, and education. Move information gathering outside of the pivotal groups, update labeling on true failure rates, on true side effects, and inform women on what can happen when this device fails. These side effects are real, and our experiences are real. I know this because I was implanted with Essure in January of 2008. I was fully occluded; I was deemed a success. And 4 months later I started getting my period every 10 days.

Three months after that, I found out I was pregnant by an at-home test in my bathroom in the middle of the night. Because I had no idea what was going on, I went to the emergency room. The emergency room had never heard of Essure, and my doctor had never had anyone become pregnant. Four months after that, during a routine ultrasound, we found shadows on my uterus. Unfortunately, at that point, I couldn't go through any other further testing. I was pregnant. But we did guess that the coils had either moved or migrated or were expelling. The tech was baffled.

Early 2009 I experienced my high-risk pregnancy, getting monitored every 10 days, ensuring that my baby was growing. I did deliver a healthy baby girl in July of 2009, but unfortunately, in the first 2 years of her life, she developed a blood disorder.

From 2009 to 2011 my health quickly declined. I had migraines for the first time in my adult life. I had psoriasis covering my head and my shoulders, my fingernails and my toenails. I had hives and rashes. The autoimmune responses that I was going through, not

one doctor could figure out how to help me. I spent 3 months with the Mayo Clinic trying to understand a hemifacial spasm. The Mayo Clinic sent me home and said I was stressed. They had no idea what to do.

On October 11th, 2012, we found a softball-sized tumor in the center of my chest, and I was diagnosed with Hodgkin's lymphoma. For years I was sick. Specialists, doctors, the best of the best could not tell me what was going on, and I simply called an allergist. I found out that I was allergic to nickel. And in March of 2013, while I took out a portacath for cancer treatment, I had a hysterectomy to remove Essure.

It was the FDA's job to protect us and to inform us and to ensure we knew what we were getting ourselves into. That didn't happen, and I would like to know why.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: Can we have Speaker No. 42? And then we'll go back up after that. But as you work your way up, just let us know your name and your affiliation.

MS. PITT: My name is Sheila Pitt. I'm here on my own, with no financial assistance. I am a private citizen. I'm here today as a wife, as a mom, a face to an adverse report, and as a woman who thought I would have Essure permanent birth control in me permanently, but I had it for just over 9 years.

My story is pretty simple. I got Essure in 2004, and I had it removed in 2013 after seeking help for unexplained issues similar to those described by the others today. I'm sorry, I'm very nervous. Within the first few days after my major surgery for removal, I felt

better than I had in years. At the time I didn't really know and understand what happened. Even my sense of smell returned. I had lost it in 2011, with no explanation. I am not a medical professional. I ask the Panel, when considering all the questions, that everything that you talk about today and any information changes be given to people that currently have Essure, not just those who are considering Essure. It seems to me that adverse effects of pain, migration, and even developing metal sensitivity have been added to the list of Essure side effects on different websites.

Although I no longer have Essure, my question and concern is for those that I know personally, and here today, who know so many other people. My concern is will any recommendations made today be communicated to women who have had Essure for years? How about the adverse events that have been talked about today? How are women going to know if they have an adverse effect? They don't even know what they are. I think information needs to be given to current Essure patients and, as we've discussed already today or heard, information to be given to patients considering Essure.

The Panel has seen, in my opinion, that little info on identifying side effects in women that have Essure for years, like over 5, 10 years -- I'm saying that I don't think there's much that exists. For something that is meant to be inside for 50 years, I feel that current, not just future, patients need information. As many women may not return to their implanting doctor for various reasons, I think that all medical professionals need to know about Essure side effects discussed today, and ways for removal.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: We're going to go back to Speaker No. 39, please. And I think those slides are ready now. So I'd like you to also state your name and your affiliation.

MS. RUSMISELL: Can the technology people just let Carrie know where she needs to point the clicker so that it works?

My name is Amanda Rusmisell. I'm from Charlotte, North Carolina. I have no financial conflict of interest.

I had Essure implanted in December 2008 during the most painful procedure I've ever endured. After this, my life was altered by pain and debilitating periods until I had a total hysterectomy because of Essure. The 20,000 members of our Essure Problems group have been impacted in many ways. I am here to discuss how Essure economically impacted us. Specifically, we're going to look at the out-of-pocket expenses that our members reported on a survey that covered the time from implantation to removal.

First slide, please.

This is implantation. We had 229 women participate in the survey. Essure is sold as a low-cost procedure. Only 30% of our survey had out-of-pocket expenses.

Our next slide is confirmation tests. We had 164 women have some type of confirmation test. Some did not have the test because it was not covered by insurance. Out of the 164, we see that 34% had out-of-pocket expenses. Essure is costing the patient more.

Our next slide is doctors' appointments due to complications. Two hundred and fourteen women from our survey had doctors' appointments. This looks at all primary care

and specialist appointments. Now we see the jump; 67% had out-of-pocket expenses.

Our next slide is emergency department visits. One hundred and thirty-three surveyed had emergency department visits, emergency visits for things like extreme pain and heavy bleeding; 57% had to pay out-of-pocket expenses.

Our next slide is tests to diagnose complications. One hundred and eighty-two women from the survey had diagnostic tests. Some examples are blood tests, ultrasounds, radiology imaging, and allergy testing; 52% had out-of-pocket expenses.

The last slide is Essure removal. From this survey group, 113 women have had Essure removed; 64% of them had out-of-pocket expenses for removal. Remember, this is up from only 30% having out-of-pocket expenses with implantation.

This is just a small peek into the financial impact of Essure. We were told that Essure was low cost. These statements demonstrate that Essure was anything but low cost. Essure cost us financially, physically, and emotionally. Every woman should have the right to a safe, effective, and affordable birth control. This is not the case with Essure. The FDA failed us, and the FDA failed our families.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I invite Speaker No. 40 to the microphone. And I think those slides are ready. They're not. Okay, pardon me.

We will then move on to Speaker No. 43 while we resolve that issue. Speaker No. 43. There you go.

(Off microphone comment.)

DR. IGLESIA: Take your time. Just state your name and your affiliation.

MS. GREAGER: Hi. Good afternoon. My name is Alicia Greager. I am not here with anybody or affiliated with anybody, and absolutely nobody gave me any money, nor will they when I get out of here.

What Bayer has said, I was the perfect candidate for Essure. In June of 2008, I went to the gynecologist. I chose to have permanent sterilization. With the recommendation from my doctor, I fully consented and thought I understood everything, and I really and honestly thought that Essure was a perfect solution for me.

Within a few weeks I went back. The surgery was okay. I was asleep, though, I believe, because my insurance paid for it. And a few weeks later I went back, I had a couple follow-ups, I was bleeding a lot. She said, oh, you know, that's going to take a while, that will take a while, that will take a while. I said okay. It took a while. Well, it's 2015. I bleed every 12 days, every 12 days, with massive cramping, clotting. I now have rectal bleeding too, which is fun. I have hair loss, which my grandchildren lovingly crawl right through and wrap themselves in. I lost four teeth, literally popped out of my mouth. Don't know why. I have no clue.

I have excessive sweating, which is lovely, lovely, lovely. Walking around and people randomly walk up to you and say, ma'am, are you okay? I'm fine. My heart rate is at resting, and when I say resting, I mean when I wake up in the morning, 90 beats per minute. Hasn't changed. I've been hospitalized, and they thought I had a stroke. My daughter had to come to the hospital, and she was in the Marine Corps at the time. She runs down to the hospital, and she comes to me thinking I'm dying. They can't find anything besides the

stroke symptoms, but no signs of an actual stroke.

I have a medical record, which I didn't bring with me today only because it's a public hearing, that will show you, without a doubt, a clear path from my history, which I have all the way from when I was a child to now. It is the Essure, whether I have an allergy to it, which that's another fun thing. I have nice skin itching. That's great. And little boils that pop up everywhere. I have problems with pain every day. Twitching. That's another fun one. And one of the worse things about the whole thing is I have to smile and be happy and move on. And it's really hard. I had to adapt to that. I had to adapt to all of those things. And now, today, I want to tell you how important it is that I'm here. Right now, at this very moment, my daughter is in Washington where I came home from, I live in Pennsylvania, and she's in labor with my third grandchild. And I'm here because my whole family supports me to do this.

I believe you should recall it. Bayer, I 100% believe you should set up some kind of fund for us and please take them out of here. You know, the Panel, I think that you should tell the FDA -- I trust them, I do. They stamp my meat, I love meat, and I think you should advise them to do something for it.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 44 to the podium. And please state your name and affiliation.

MS. HUGHES: My name is Kimberly Hughes, and I have no financial conflicts of

interest to report.

My Essure procedure was done in 2009 in a hospital, with anesthesia, and I wasn't asked about metal allergies because if I had, I would have refused the procedure. The years that followed brought pain, confusion, doctors without answers, and two major surgeries. My side effects included constant pelvic pain, dizziness, ovarian cysts, heavy and painful periods, periods lasting half the month, anemia, vitamin D and B12 deficiencies, weight gain, abdominal swelling, and eczema on my hands, all problems that didn't exist prior to getting the Essure procedure done.

In late 2011, after more complaints of pelvic pain, a CT scan and ultrasounds revealed a 10 cm cyst on my right ovary. So I had surgery to remove the cyst and the ovary, but the pain continued. Dizziness led to two falls down flights of stairs. The fall in 2011 resulted in injury to my coccyx and lower back, making it painful to sit or stand for any length of time. The fall in 2013 resulted in a concussion. Post-concussion syndrome has left me with frequent migraines, memory problems, difficulty with word recall, multitasking, and concentration, as well as light sensitivity, confusion, difficulty remembering new information, noise sensitivity, mental fatigue, sensory processing problems, brain fog, and one pupil larger than the other.

More than 10 doctors and dozens of tests later, I still didn't have any answers. None of them put the pieces together. But the simple names of the side effects and problems don't even begin to illustrate the occupational, social, financial, and psychological impact they have on a person's life. And that's the true impact of Essure. It wasn't until I found a group of thousands of other women who have been suffering from the effects of Essure

that the struggles I had been going through for the past 6 years began to make sense. I found this group of women when I was searching for answers when my period began one day and just never stopped. I was very anemic and weak, and I didn't know what was happening.

I had to have a hysterectomy in June of this year. The pathology report showed that there was extensive endometriosis and adenomyosis. A hysterectomy was my only option by the time I put the pieces together. I may have been able to get rid of the constant pain and bleeding and some of the allergic reactions; however, I'll have to live with the life-altering effects of chronic back pain and post-concussion syndrome.

The simple procedure that Essure was billed to be turned out to be the most devastating mistake I have ever made. I have no doubt there are thousands more women suffering that have no idea that Essure is the cause, because their doctors are not connecting the dots or taking the complaints seriously. Other victims of Essure are the only hope for them right now because the FDA has failed to warn and protect them properly.

This device needs to be taken off the market now before more women are harmed, and Bayer needs to be held accountable to all the women who have suffered with Essure.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I'd like to invite Speaker No. 45 to the microphone. And if you could state your name and affiliation.

MS. SCANLAN: Good afternoon. My name is Susan Scanlan. I'm President of the Women's Research and Education Institute, or WREI, which has provided timely nonpartisan

policy analysis to the women in Congress since 1977. For 9 years, from 2004 to 2013, I served as chair of the National Council of Women's Organizations, a coalition of 240 progressive women's groups representing 12 million American women. Women's health and reproductive rights were at the top of the National Council's agenda.

I have accepted no payment to speak here today and have no financial relationship with Bayer. It's my job this afternoon to tell you how critically important it is for women in the United States and around the world to have access to safe, effective, and affordable permanent birth control, birth control that Essure provides to so many.

Essure represents a vital and growing reproductive option that has been successfully performed on more than 800,000 patients over the past 13 years. A recent practice bulletin issued by the American College of Obstetricians and Gynecologists recognizes that hysteroscopy tubal occlusion for sterilization has high efficacy and low procedure-related risk, cost, and resource requirements.

Of course, all of us are concerned about possible side effects that are being raised today. We're not just concerned; we're heartsick. We do not discount any individual's personal claims or suffering, but no form of birth control is without risk or should be considered appropriate for every woman. It is important that female patients discuss all risks and benefits with their physicians and adhere to all medical protocols. It seems to me that a lot of them have gone in uninformed, and that is not right.

It is equally important that data about possible side effects be collected and analyzed in a careful and irrefutable way. Such scientific fact finding has not occurred in the case of Essure, and a fearful message is being sent to people who might most benefit from

it. My concern is that access to this proven medical device could be limited or even denied to women who want and need it. The market shows that American women are looking for permanent birth control that is simple, reasonably priced, and does not require a lot of recovery time, that can be performed in their doctor's office, that does not require surgery or exposure to its potential risks, and that does not contain any hormones. Essure does answer every one of these requirements. American women have the right to make an informed decision to use it.

I thank you for listening to me today. You have a set of tough decisions ahead of you, but I'm confident you'll find a way to balance majority needs against the compelling, tragic stories that these brave women have told us today.

DR. IGLESIA: Thank you very much.

And, finally, I'd like to go back to Speaker No. 40. And I think those slides are ready, and this is our final speaker. And if you could just state your name and affiliation. Thank you very much.

MS. CERVANTES: My name is Christine Cervantes, and I have no financial conflict of interest. I traveled from Lake City, Texas to be here to speak today.

I was a 39-year-old mother of four when I talked to my gynecologist about becoming sterilized. I requested a tubal ligation, but my doctor was quick to recommend Essure as a safer, nonsurgical option. I told my doctor that my only concern, since she had assured me of its safety, was of migration. My younger sister had had Mirena, and it had migrated into her abdomen and had to be surgically removed. I did not want to have a similar experience as my sister. My doctor assured me that migration couldn't happen due to the scar tissue

forming around the implant and holding it in place. She said the migration warning on the pamphlet was standard because it was a medical implant.

At the time of my HSG test, it was confirmed that my left implant was in place and my fallopian tube had occluded. My right implant was shown to have migrated and, per my report, was in my abdominal cavity. I immediately contacted my gynecologist, very upset. Her initial response was to repeat the procedure, putting another implant into my open fallopian tube. By this time I had started noticing changes throughout my body, side effects, if you will. And not only did I not want another Essure device put in my body, I wanted the two existing Essure implants taken out.

My gynecologist then contacted Bayer to find the proper protocol to remove Essure and was informed that there was no protocol for removal once migration had occurred. She informed me that she was no longer willing to perform the surgery and forced me to become my own advocate. After calling numerous doctors, I found a gynecological oncologist that would take my case, even though I did not have cancer, because she was experienced with complicated surgeries.

During my LAVH-BS, it was discovered that in fact both of my Essure implants had migrated, and both were protruding through my uterus. You see, there is a complete disconnect between doctors and patients when it comes to their response to migrations, complications, failures, and side effects. If doctors are not being trained to handle the complications that can and will arise, then they have no business implanting women with these medical devices.

As a victim of Essure, I'm here to say enough. Women deserve and demand better

than what these devices are doing to our bodies and to our lives. I'm asking Bayer and the FDA to remove Essure from the market.

Thank you.

DR. IGLESIA: Thank you very much.

(Applause.)

DR. IGLESIA: I apologize, but there were two speakers that were absent. I'm going to just give them one last chance, if they're present, to come up to the podium. One was Speaker No. 10, Michelle Garcia. And the second was Speaker No. 25, William Myers.

MS. MYERS: Williams Myers is my husband, and we couldn't afford to pay for him to come.

DR. IGLESIA: Thank you.

(Off microphone comment.)

DR. IGLESIA: Okay. Well, thank you then.

At this time, if we could get the lights back on, I'd like to ask our Panel members if there are any Open Public Hearing speakers -- that they have any questions at this time. Yes.

DR. CHAPPELL: Brief questions or brief clarification?

DR. IGLESIA: Correct.

DR. CHAPPELL: I have one for Mark Bell, if he is still here. And I'm supposed to announce my name, right? Rick Chappell. Yeah.

(Off microphone comment.)

DR. IGLESIA: Okay. Yes, this will be the only opportunity before we reconvene as a

Panel. Are there any other Panel members that may have brief clarifying questions for our speakers this afternoon? The public speakers.

Deb.

DR. MYERS: Deb Myers.

Speaker Laura Russell, Medsurge, if still here. In your presentation you talked about blood tests for screening patients. I was hoping you could give additional information on that.

MS. HENZE RUSSELL: I will follow up in writing with more detailed information on the screening for medical devices. I'm familiar with similar screening tests for tolerance versus toxicity for dental materials, because I had that a blood test can tell you which materials you are highly, moderately, and least reactive to. And I know this because I was sick for 20 years from mercury from dental amalgam, which is how I got introduced to metal toxicity issues with devices. I've been trying to track that down because I've been told by people who have done orthopedic procedures that there are tests that can be done. Are there any physicians in the audience who could address that?

(Off microphone comment.)

MS. HENZE RUSSELL: Orthopedic Analysis does specific Essure testing. And I believe that there are tests that can be done for basically any or all medical devices, and I think that's something we should all learn more about and recommend, if not require, before devices are installed on a non-emergency basis.

DR. IGLESIA: Thank you very much.

DR. MYERS: Thank you.

DR. IGLESIA: Dr. Chappell.

DR. CHAPPELL: Yes, thank you.

I have a question for Mark Bell. Could you please clarify -- and I'm sorry if you already said this -- whether the photo micrographs of Essure that you presented were new products or post-implant or a combination.

MR. BELL: Everything was post-implant.

DR. CHAPPELL: Thank you.

DR. ELSER: Denise Elser.

This is for -- I think it was Ms. Reed who is an immunologist, is that right?

UNIDENTIFIED SPEAKER: Dr. Reed.

DR. ELSER: Dr. Reed? Sorry. Because we hear a lot of symptoms that may be related to some type of -- are you saying it's like having a rheumatology office? These are likely autoimmune diseases that we're seeing, or symptoms. Is there any testing to link a correlation or any others outside of these symptoms and the timing of the procedure?

DR. REED: So one of the things that makes it very difficult to prove cause and effect -- and even if you look at diseases that we have a much better handle on, like lupus and rheumatoid arthritis, people really can present with a spectrum of symptoms, and there's no one symptom that you say aha. Even with rheumatoid arthritis, some people get joint pain, some people have high levels of rheumatoid factors, some don't. In a case like this where, like we said, that the mucosal immune response is not well understood in animals much less in this sort of setting, that there's no -- I can't think of a single -- I mean, you could look for inflammatory markers, and I bet you'd be high in every one of these women,

but that doesn't really tell us anything prognostically.

DR. IGLESIA: Thank you very much.

Okay, there being no further questions, I want to take a moment to acknowledge and thank all of those who came to speak at our public hearing. The Panel realizes how difficult it is for you to travel here at your own expense and to share your personal stories with us about your experiences with Essure.

I now pronounce the Open Public Hearing to be officially closed. We will now proceed with today's agenda, and during that deliberation, at the request -- at my request, we may be able to take some further questions from the presenters.

But at this time we will take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members inside or outside of the audience. We will resume at 3:59.

(Off the record at 3:49 p.m.)

(On the record at 4:10 p.m.)

DR. IGLESIA: If everyone could take your seats, we will begin the Panel deliberation session now. So we will now begin the Panel deliberations. I want to open the floor to the experts around the table to begin deliberating on any thoughts that you may have with any information you have heard today or the material that you have read in your Panel packets.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair.

Now, first, do any of the Panel members have any questions or comments for FDA or Bayer HealthCare before moving on? I know that there were two. And please be reminded

that during this time, persons may only approach the podium when directed by the Chair.

So I know that Ms. De Luca had a question, and Dr. Seifer had a question specifically to the FDA. So we'll start with you, Ms. De Luca.

MS. DE LUCA: Jo-Ellen De Luca, Patient Representative.

I was wondering if the women that have problems generally, if they go to the same physician. So if they are going through the Essure process with a physician, do they keep that same physician? It seems to me it would be a bad move to then go to physician Y and then Z to prevent the problems from happening in the first place and keeping track of anything wrong.

DR. IGLESIA: So does the FDA have any information, Dr. Yustein et al., on lost to follow-up where a patient is an index case and may have a problem but does not see the same implanting surgeon?

DR. YUSTEIN: I don't think that's information that we normally collect. It might be worth asking some of the audience members who have presented today their experiences.

MS. DE LUCA: I guess I'm looking if some of the poor performers are people who neglected to go to their physician in the correct follow-up manner.

DR. IGLESIA: I know that that was mentioned --

DR. YUSTEIN: Right.

DR. IGLESIA: -- on the -- in the public hearing portion.

DR. FISHER: May I? Real quick. Actually, there were a couple questions that were asked before lunch that we have prepared answers to, and I believe that one of those --

DR. IGLESIA: Was Dr. Seifer's.

DR. FISHER: One of our responses kind of addresses that question, and it has to do with the lack of follow-up. So maybe if we -- before we get into additional questions, maybe if we had a chance to respond to the questions that we had.

MS. DE LUCA: I'm looking for follow-up in an explicit way, not just go to Dr. Smith and then go to Dr. Somebody Else, get another answer, and never probably getting their original problem seen and followed.

DR. FISHER: So I understand your question. That is not information that we have. But, once again, I think that some of these patients, from what I've heard, it sounds like they have gone to multiple doctors, but that's not information that we have.

DR. IGLESIA: But I do recall that Dr. Seifer was the one who had the initial question about some of the complications. Is that what you had to prepare?

DR. FISHER: Well, there were three questions, and if you don't mind, can I go ahead and --

DR. IGLESIA: Please address.

DR. FISHER: -- try to address those?

DR. IGLESIA: Please.

DR. FISHER: Okay. So there were three basic questions. I want to start with Dr. Coddington, and it had to do with lost to follow-up. And lost to follow-up can be interpreted a couple different ways. True lost to follow-up -- I think your question to FDA was, do you get additional information on patients? Can you get additional information from the company on lost to follow-up? And we can request additional information, but usually lost to follow-up is lost to follow-up, and there's not a lot of information that comes

with those patients. Now, I will say that going back and looking at the IDE studies, true lost to follow-up, there were only three patients that were lost to follow-up, okay? But I would like to make a distinction here because there's also something that has to do with patient discontinuation.

And if you look at the Executive Summary, Table 4 is on page 16, and it talks about events that delay and prevent the reliance on the Essure device for contraception, and it lists a couple different reasons why a patient may not continue on in the study. They would still be followed, but it has to do with perforation, expulsion, maybe they got a unilateral implant, I think. And I can ask the company if they would like to clarify this. Probably the only patient that they wouldn't follow would be one where they couldn't get an insert in at all, okay? So that's where there's a little bit of difference there between loss of follow-up and discontinuation with patients.

Now, when we talked briefly, there was also the question kind of like lost to follow-up. What happens with a patient during that compliance period where you lose them? This is a method, so they have to come back for that confirmation test. And one of the things that we had presented, we had presented ranges of patient confirmation, and it ranged from 28% to 100%. Now, the information that we have is from the scientific literature, and I'm going to ask Allison O'Neill to come up, and she can put the slide up to show you where we're getting these numbers, okay, because these were not part of the IDE. These are non-sponsor -- non-company sponsored studies. And in addition to that, I think she has some information as to some of the reasons behind why patients failed to come back for that confirmation test.

MS. O'NEILL: So I believe it's the next slide, please. Yes. So this is a slide that shows some of the compliance rates that we found in the available literature. This represents studies from both the U.S. and outside the U.S., so it's not exclusively HSG. But this is where we got those ranges that we presented.

The first two references with the lowest compliance rates, both represent clinic populations where a majority of the patients had public insurance. And in reviewing those two references, we found a couple of reasons that patients may not be compliant with HSG, including health insurance coverage or lack of. Second, the patient may be responsible for scheduling their own HSG with a radiology unit, especially when there's a lack of patient tracking or follow-up by a staff member. And another reason could be scheduling difficulties between -- coordinating between the gynecology and radiology unit and possible inconvenience related to that. So this is just a quick snapshot of kind of a spectrum of compliance rates, and a little bit more detail can be found in Appendix A of our review memo.

DR. SEIFER: Do you have any estimation about the lack of insurance coverage for the HSG? In other words, was it more than half of the noncompliance that could be explained by that?

MS. O'NEILL: I believe in the first study it wasn't half, but it was the first -- it was the most common reason.

DR. FISHER: Okay. And then I think that there was -- thank you, Allison. I think that there was a third question that Dr. Milner had, and it was in regards to metal allergy or allergic reactions and how it was defined during the IDE studies. And we went back, and we

looked at that, and there was no solid definition of reporting an allergic reaction. But I would like to bring Dr. Corrado up, if I could, please, to provide some insight as to when we started looking at this issue of some of these other symptoms and considering could it be an allergic reaction and some of the things that we did.

So, Dr. Corrado, could you come up?

DR. CORRADO: So I'm just going to very briefly say that it's our recollection that we were not explicitly advised of nickel allergies in the Phase II and pivotal studies at the time of the premarket review. However, in approximately 2011, in one of the PMA supplements, we were discussing labeling around potential nickel allergy, and the Sponsor at the time, Conceptus, informed us of the following:

Records of over 650 women in the Phase II and pivotal trials were reviewed for adverse events potentially related to nickel allergy. The women were followed for up to 5 years after being implanted with Essure micro-inserts. There were no chronic reports of skin rash or itching. Four reports of itchiness, hives, rash, or eczema occurred that were not attributed to another cause. All were of short duration and resolved with medication. Micro-insert removal was not required for any of those reports.

So that was the information as it evolved from the premarket review to postmarket.

DR. MILNER: So just so I understand, so they were thought perhaps to be related to the insert; is that correct?

DR. CORRADO: Basically by default. They could not be attributed to anything else.

DR. MILNER: Okay.

DR. CORRADO: And so what the Sponsor was trying to do at the time was say we

didn't identify anything as an allergy per se. However, we went back on records, and we found these four symptoms, essentially signs or symptoms, and we're telling FDA -- we're telling you about that because they could be evidence of nickel sensitivity.

DR. MILNER: Okay. But then what was the criteria that was used to decide what is an allergy?

DR. CORRADO: That is a question I am unable to answer. I'm sorry. Maybe the company would like to take a crack at that one.

DR. IGLESIA: Would you like to address that?

DR. MILNER: If there's an answer, yeah, sure.

DR. IGLESIA: Would Bayer like to respond about the allergy issue? And just please state your name.

DR. ZAMPAGLIONE: Sure. Great, thanks. Edio Zampaglione, Bayer HealthCare, U.S. Medical Affairs.

No, there was no criteria per se in the studies to identify or to say this is an allergic reaction. So we also do not have that.

DR. MILNER: So how is it that you can declare that there's no allergy if you don't have a criteria for whether there's an allergy or not?

(Applause.)

DR. ZAMPAGLIONE: So the symptoms that are with these allergic reactions, they're broad. There are so many different etiologies. We're exposed to so many different types of chemicals, of foods, et cetera. It comes down to clinical understanding and clinical judgment with these and trying to determine is this due to the inserts or potentially due to

something else? And it seems to us that it ends up being an exclusion at the end of the day, that you just rule out what it is and what might be the cause, and then you're left with, you know, in the cases that I'm hearing, possibly that it's the insert. But it still is very rare from all the data that we have seen and looking at the literature.

DR. IGLESIA: Dr. Schalock.

DR. SCHALOCK: Peter Schalock.

My question is this, how can Bayer and the FDA have no knowledge of nickel allergies when the original package insert prior to 2011 -- at least my quote from my own talks state that a contraindication is a known hypersensitivity to nickel confirmed by skin test. How do we not have data on this?

DR. IGLESIA: Is that a question for Bayer or for the FDA?

DR. SCHALOCK: It was a question for anybody who will answer it. How do we not have data on nickel allergy when we have a device that's 55% nickel, and 20% of women -- approximate numbers -- are known to be nickel allergic? Why is there no data? How can you put this in your package insert and then have no clue?

DR. IGLESIA: I just want to remind everybody, even when you come back to the mike -- and I'm Dr. Iglesia -- that we have to state our name each time for the transcriptionist.

And I'm going to invite Dr. Zampaglione or anybody else from Bayer, if you have an answer to that question from Dr. Schalock.

DR. ZAMPAGLIONE: So Edio Zampaglione, Bayer.

The skin test, the requirement for that has shown that there's no correlation. From the studies that were done by Dr. Zurawin in 2011 that was published, there was no

correlation. You know, you're talking about dermatologic reactions as compared to something that's inside the body. But let me bring up one of our allergy specialists who can help shed some light on this as this is not my extreme area of expertise.

Could I have Dr. Hamilton, please?

DR. HAMILTON: Hi. Robert Hamilton, Johns Hopkins University School of Medicine. I am a Professor of Medicine, and I oversee a diagnostic allergy laboratory.

Allergy, for me, is immediate-type hypersensitivity. So the definition really has to be clearly defined. And when we're talking about T-cells, we're talking about slightly different. So for those that are not immunologists, there are four types of hypersensitivity, and three of them involve antibody. Today we're talking really about T-cell responses or Type IV hypersensitivity. So I take a quote from Dr. Schalock's nice review where he said, basically, that either cutaneous or systemic reactions can occur from implants, even though they're very rare.

And so if I could have the first slide, please.

So we've been already told, both by Bayer and by the FDA, that nickel released from the Essure device is actually very minimal, and compared to levels that are released from other devices and also from environmental exposure, they're very, very insignificant.

So if I could have Slide No. 2, please.

So if we can define nickel allergy as an exaggerated immune response that only occurs in genetically predisposed individuals when exposed to nickel, the key here is high exposure and genetic predisposition. It occurs most commonly after skin contact to nickel, and the most common exposure we have in the environment is to nickel jewelry, where we

get a contact dermatitis. In fact, I have a Type IV hypersensitivity to nickel due to a ring I bought. Another example of contact dermatitis is poison ivy, which involves the contact of urushiol from the actual plant itself.

And nickel allergy is mediated by the white blood cells, called T-cells for those of you that are not immunologists, and classified immunologically, as we mentioned, as a Type IV hypersensitivity. And there are four classic symptoms of a Type IV inflammation associated with Type IV hypersensitivity, and those are swelling, redness, heat, and pain. And I believe these are the four symptoms that have been used to select the criteria for trying to define whether the observed symptoms were in fact "latex allergy," which I would like to suggest now we talk about as -- I mean nickel allergy. I suggest we talk about it as nickel sensitivity or hypersensitivity at this point.

DR. IGLESIA: I'd like to ask if Dr. Wills-Karp has a question, and then we'll get back to you, Dr. Schalock.

DR. WILLS-KARP: I think your --

DR. IGLESIA: And just introduce yourself again.

DR. WILLS-KARP: Marsha Wills-Karp.

I think your points are well taken, and as you pointed out, the nickel sensitivity is lower, although in my reading of it, it's increasing with increasing exposure of the population by piercing and earrings and other things. The incidence of nickel sensitivity is increasing. But, in the population of the studies you did, you might not have picked it up or had the power to detect it because it is a very small population, but it does seem that listening to today's conversation, that it's worth going back and revisiting this and taking a

look at it, so that if some of these side effects are really attributed to that, that could be put as a contraindication to the use of this device. It's not clear at this point whether all the symptoms that were being reported are due to that, but it's possible and it's unknown. So I think there needs to be some further analysis of the data.

So I don't know if I can do this, but how many people in the audience actually know they're allergic to the nickel?

DR. IGLESIA: I have to ask the questions.

DR. WILLS-KARP: Oh, I'm sorry.

(Laughter.)

DR. WILLS-KARP: That's why I said I didn't know if I could do it.

DR. IGLESIA: Yeah, that's okay. I'm going to go with Dr. Schalock here for a second, just to finish up the conversation.

DR. SCHALOCK: I'm going to reiterate the same question I asked before. You -- well, Conceptus, maybe not Bayer -- listed initially to consider testing for nickel in patients pre-implant. I may be paraphrasing too broadly. Where is your data? Where did you test these people? How did you test these people? What did you test them with? And what in the world happened to that information, or does it not exist?

DR. IGLESIA: So, to paraphrase, you're asking about what kind of screening was done prior to implantation, if any, on instructions for use?

DR. SCHALOCK: Well, considering that they listed it as a contraindication themselves. At least from my understanding, if they're listing it, are we just making this up just for fun, or is there data? Do we have data? That's what I want to know.

DR. IGLESIA: And does Bayer have any information about the screening for such, since it was listed as a potential relative contraindication?

DR. ZAMPAGLIONE: Sure. Edio Zampaglione.

Let me call up Dr. Kimberly Rosen. She's head of our clinical development group for Essure, and she will hopefully be able to answer that.

DR. ROSEN: Thank you. Kimberly Rosen, global development.

So I don't think I can exactly answer your question, but I can at least explain how the initial protocols were worded with respect to metal or nickel allergy, which is there were no contraindications and there was no screening in advance of entry into the Phase II or pivotal studies for nickel allergy. We were not, as a sponsor, involved at the time of the initial PMA approval with discussions in terms of what was included in the initial contraindications, but there were no in- or exclusion criteria related to nickel allergy for the pivotal and Phase II studies.

DR. IGLESIA: Dr. Milner.

DR. MILNER: Josh Milner.

I just wanted to get back again to the question about allergy. Certainly, from an allergist's point of view, we do like to be very, very careful about what we call an allergy versus a Type IV hypersensitivity, which is not mediated by IgE, which is not necessarily mediated by mast cells, and it does cause a tremendous amount of confusion to patients. For them, it's all the same thing. And I agree that those do need to be separated. But, either way, the patient needs to know about both things. So they need to know about if there is a Type I hypersensitivity and there are clear criteria for that, and if there is a Type

IV hypersensitivity and there ought to be clear criteria for that, which would be laid out a priori in any instance of contact to something like that. And I think that's -- otherwise you get a zero, which is not true.

(Off microphone comment.)

DR. IGLESIA: Dr. Myers.

DR. MYERS: Deb Myers.

A question. Are we aware of any animal models or any sort of basic science models that involved nickel? Not skin contact, but within the body cavity. A general question.

DR. IGLESIA: And that's a question for Bayer or FDA or other?

DR. MYERS: Other.

DR. IGLESIA: Dr. Corrado or Ben? Because you mentioned the 2012, the four cases that potentially could have had some relationship to the implantation device, did that spawn any more basic science research in this area?

DR. FISHER: So I know that there was traditional biocompatibility testing done for -- with the PMA. Most of the biocompatibility testing came back negative. The one that came back positive had to do with -- I believe it was the muscle implantation, but I have a gentleman behind that will correct me if I'm wrong. But it had to do with, I believe, the PET fibers actually being able to initiate that ingrowth. So it wasn't something that was surprising to us.

DR. IGLESIA: So the PET is the polyethylene terephthalate coating.

DR. FISHER: That's right.

DR. IGLESIA: So would that person like to address that topic right now?

DR. FISHER: Ron, do you have anything that you can add to that?

(Off microphone response.)

DR. IGLESIA: Would you like to come to the microphone?

DR. FISHER: No, I don't think that he has -- well, I shouldn't speak for him.

(Off microphone comment.)

DR. IGLESIA: You have to come to the microphone and introduce yourself.

DR. BROWN: Ron Brown, toxicologist, CDRH.

Actually, Dr. Fisher, I hadn't had the opportunity to see those data. And so my efforts on this device are really focused on the potential risk of adverse effects occurring from the nickel exposed to the device. So I haven't had a chance to look at those data.

DR. FISHER: Okay. Thank you, Ron.

So I don't know that any of the biocompatibility testing or any of the animal testing specifically addressed an allergic response, and I am not the person to say what an appropriate model for something like that would be.

DR. CHAPPELL: May I follow up?

DR. IGLESIA: Let's just go down the line. I know that Cynthia --

DR. CHAPPELL: It's similar.

DR. IGLESIA: Okay. If we're on the same topic, I'll let you go, Dr. Chappell. And introduce yourself.

DR. CHAPPELL: Rick Chappell.

On the same topic of sensitivities to polyethylene terephthalate, besides reactions to the organic compounds in it, there is a metalloid element, antimony, which is used as a

catalyst in its production. And I know of that because there is what many countries consider excessive levels in juices and other liquids that are used. They're used for beverage containers, which makes me a bit worried about having it contact with -- constant contact with an internal organ.

(Applause.)

DR. CHAPPELL: Will that worry may be justified? I don't know. But I would be interested in data to see if there is any evidence of antimony leaching, and that can be determined from blood samples or other kinds of very direct and relatively cheap measurements. So the question is whether that has been done or contemplated, and it's directed to the FDA and Bayer.

DR. FISHER: And I would say that that was not part of the information that was provided with the PMA.

DR. IGLESIA: And Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

My question sort of follows Dr. Chappell's. I'm wondering about the percentage of nickel to other metals in the device. I'm wondering if there has been any looking at the interaction of those metals with each other that may cause something to happen. And putting this metal device in a soft tissue organ seems to me to possibly be different. They brought up other implants, but this is different from those others, I think. So I'd like to hear from the -- no. Immunologists? Allergists -- about these things. Or the toxicologists. I just think there should probably have been more pre-human studies and --

DR. IGLESIA: And would you like to start with the FDA or with Bayer?

MS. CHAUHAN: I'm open.

DR. IGLESIA: Okay.

MS. CHAUHAN: Whoever would like to start.

DR. IGLESIA: Well, let's start with Bayer, for the allergists and/or immunologists, the gentleman from Johns Hopkins perhaps. And the specific question is the metal on metal and direct contact with mucosal surfaces.

MS. CHAUHAN: Metal on metal, percentage of metal to metal, for direct contact with an organ in the body as opposed to a bone implant or something like that.

DR. HAMILTON: Okay. Dr. Hamilton, Johns Hopkins University.

When metal ions are released, they're actually targeted to proteins that contain sulfhydryl groups. So we know that they attach to proteins, and as such, they could come from haptens to actually intact proteins that can be viewed as foreign by the immune system.

In terms of metal on metal, we don't have any -- I don't have any data that really speaks to that issue. But we do know that when metal ions are released, they target to proteins that contain sulfhydryl groups. And therefore you can argue that a metal ion released from a device and a metal ion that is ingested in food could very well form the same interactions with proteins, and therefore, they might very well represent similar exposures. Does that address your question?

MS. CHAUHAN: It addresses it. It doesn't completely answer it. It just seems to me that more testing should be done. I don't know if the FDA has something they want --

DR. IGLESIA: Dr. Fisher.

DR. FISHER: Yes. Before you sit down, could I ask a clarifying question? I'm sorry. Then I promise that I'll bring the FDA guys up. But speaking to metal allergies, is there a level of nickel that if you go over is safe, and if you go under you're not going to have a problem?

DR. HAMILTON: Well, I believe that the Academy of Sciences has defined 35 µg/day as safe. And we do know that levels released from devices, both the Essure and also the cardiovascular devices, are well below that, which may reflect why we don't see a lot of obvious allergy. I'm not talking about IgE antibodies, but more like T-cell related responses that are very obvious. And, in fact, I know that when I got nickel allergy, it was because I had high-dose exposure from the nickel jewelry that I used. It far exceeded what I actually was consuming for many years in my food as an environmental exposure, 300 µg/day.

DR. FISHER: Okay, thank you.

And yes, I would like to call Ron Brown up to address the issue for FDA. Thank you.

DR. BROWN: Ron Brown, toxicologist, FDA.

I think you raise a very good point in general about the potential for metals to cause toxicological interactions. In the case of this device, we know that the primary metals are nickel and titanium. So titanium for the most part is biologically inert and, when combined with nickel as in nitinol, has a long history of safe use in many types of medical devices, including cardiovascular devices. So although I think it's true in general that we have to be concerned about potential toxicological interactions of metal, here's an example of an alloy that's very well characterized and has been used for many years for a number of clinical applications.

I do just want to make one clarifying point. And our colleague from Bayer mentioned a tolerable intake of 35 µg/day as being safe. I have to take either partial credit or blame for coming up with that number. And I just wanted to point out that when we derived that number, we purposely excluded hypersensitivity reactions as the basis for that value. So we believe that 35 µg/day -- and I should point out, that's a provisional value because that hasn't been published by FDA at this point. It was just derived in response to a workshop that was held 3 years ago, actually in this room, to look at the safety of nickel leached from nitinol in cardiovascular devices. So even though it's a provisional value, we were very clear that it was not intended to be protective for hypersensitivity ranges.

DR. IGLESIA: So may I ask a clarifying question for that? So if somebody does have a hypersensitivity, then that level of exposure could be much, much less. This is akin to like latex allergy. If someone is really, really allergic, I mean, just opening a pack of gloves can cause a major antiepileptic reaction similarly.

DR. BROWN: It is. And, in fact, that's a good analogy. So we recognize that there are some individuals in the population that are uniquely sensitive to certain allergens, and we don't feel that that colorful intake value is appropriately protective for those individuals.

DR. IGLESIA: Now Dr. Katz and then Dr. Baird. Thank you.

DR. KATZ: David Katz.

I had a compound question, and part of it was answered. But while you're here, is there anything unique about the epithelium in the tube, in making quantitative inferences about how much is too much, compared to the other sites where such testing has been done with other types of implanted devices?

DR. BROWN: That's a very important question for implanted devices. How does the local environment that surrounds the local tissues that surround that device, will they play a role in any toxic effects that might be manifested? I think that's best addressed by the biocompatibility testing that Dr. Fisher was mentioning. So if the device is tested in a clinically relevant environment, then if adverse effects were likely to be seen, we would hope that the biocompatibility tests would pick them up.

DR. IGLESIA: Does that answer your question, Dr. Katz? You said it was compound, so I assume there was another question, Dr. Katz?

DR. KATZ: The first part of it was already answered by the prior question.

DR. IGLESIA: Dr. Baird.

DR. BAIRD: So if this is a hypersensitivity reaction, are there ways to test for that?

DR. BROWN: Actually, since that's beyond my scope of expertise, I'm going to defer to my colleagues who are immunologists and allergists.

DR. IGLESIA: Yes, Dr. Milner, would you like to comment? Or Dr. Schalock?

DR. MILNER: Well, certainly, I'll just say from one point of view, which is sort of bets are off when it's inside the body. So you really can't say much of anything in terms of a test. There's not going to be a test that you could definitively say it's because we just don't know enough about that. One could end up finding out that a skin test has some sort of predictability, but we don't know that now. So I think that would be the most straightforward question.

(Off microphone comment.)

DR. IGLESIA: Microphone. And your name.

DR. BAIRD: Donna Baird.

It sounds like it isn't very predictive from what's already known.

DR. IGLESIA: Dr. Schalock and then Dr. Fisher.

DR. SCHALOCK: Just briefly. Peter Schalock.

Yes, I think the patch test, which is at least a skin test for nickel -- and I hope we can maybe define our terms a little bit better here. We're falling back into the term allergy. What type of allergy are we talking about? Are we talking Type I, Type IV, something else? Because they're very different things, and there are different tests for both of them. There are different cell lines involved. So I think we need to define our terms on what in the heck we're talking about. So as far as my end of things, the patch test is a good skin test for Type IV allergy, but it may not be relevant for mucosal findings, and it's kind of -- the data we have so far basically show that a positive patch test doesn't necessarily predict you're going to have a reaction when you have a device placed.

DR. IGLESIA: Dr. Fisher and then Dr. Milner.

DR. FISHER: I was just going to say, these are the issues that we're going to ask the Panel to deliberate. So, you know, if there are clarifying questions that you have for either FDA or Bayer, we'd be happy, but what the Panel is talking about right now are the exact same questions that we're going to be asking you to deliberate and discuss.

DR. IGLESIA: We'll let you get a comment, and then we'll maybe redirect specifically to FDA and Bayer.

DR. MILNER: No, it's a question, and the question is about biocompatibility studies and the question is (a) how reliable would nickel hypersensitivity be in the biocompatibility

studies that were performed in those models? And then duration as well, as it compares to the duration that we're talking about in the patients who have been reporting.

And just one last question is, whenever anyone has reported this, has pathology -- we heard one person mention pathology in the uterus, but I would be most interested in knowing what the pathology directly surrounding the device looked like upon removal in someone who removed it by choice because they wanted to get pregnant versus someone who was having adverse effects and did it correlated to their adverse effects. So I'm sorry for the three questions.

DR. BROWN: So with regard to the first question -- this is Ron Brown, FDA -- since I didn't have the opportunity to review the biocompatibility studies for this specific device, I can't answer it specifically. But, in general, we evaluate the potential for allergic reactions to occur, Type IV allergic reactions to occur, using two animal tests. One is a guinea pig maximization test, and one is a local lymph node test in mice. There are concerns about using either of these for metals, in terms of their accuracy. So I can't speak specifically about the ability of these tests to pick up a potential nickel hypersensitivity reaction.

And with regard to the second question, I think I'd have to defer to people who had seen the submission and can answer that directly. The histopathology.

DR. FISHER: So this is Ben Fisher, FDA.

So the testing, the biocompatibility was done according to ISO 10993, what was ever in place back in 2000 -- excuse me -- yeah, 2000 or when these studies were being conducted. So some of the biocompatibility testing has been changed, but I would say that actual devices were not tested for the biocompatibility testing, especially sensitization.

These were extraction studies that were done and tested in animal models. We can bring up some backup slides if you would like to see specifically what was done. It looks like you're about to get them anyway.

DR. IGLESIA: Okay, go for it. While we're putting it up, I actually do have a question, and maybe I would like to bring Bayer back in because, you know, one of the reasons why maybe they didn't screen was because they thought that the background rate of nickel allergy was so low. But my question is what rate were you going at as being so low? And also what is the potential of developing one de novo? You know, because now you're being exposed on an epithelial surface. So those are questions that I'd like answered. We will have FDA bring this up, though, first.

DR. FISHER: We could. This is just a summary slide of the biocompatibility testing that was performed for the PMA. It shows the different tests that were done. I can probably get more information if it was done on mouse or rabbit. I just want to, you know, let everyone know that these are not -- these are in vivo tests, but they're done in animal models. And I would like to say that from what I recall from reviewing the data, all the tests, the biocompatibility testing was negative, with the exception of the one test.

DR. IGLESIA: Yes, Doctor. And introduce yourself.

DR. WILLS-KARP: Marsha Wills-Karp.

Can I ask you if these studies were done in backgrounds of animals that were known to be susceptible to these type of responses?

DR. FISHER: Okay. So these studies would have been done under GLP, okay? So they are done -- usually they're done in rabbit or mice. Most of the tests were done in

mice. They're standard inbred strains. The rabbit, I'm not quite sure which actual strain was used. But most of these tests are done by a contract research organization or done in-house according to GLP. So the protocols are set for both strains and exposure conditions.

DR. WILLS-KARP: So do you have a positive control?

DR. FISHER: I cannot say if positive controls were done in these studies. Some of these -- I think some -- well, do you know if any of these require a positive control?

DR. IGLESIA: There's the mike, Dr. Brown.

DR. BROWN: Some of the test methods do require positive controls, and others don't. Generally, the in vitro ones are ones that positive controls are used in.

DR. IGLESIA: Dr. Milner, was your question completely answered on this pathology question? And then I'm going to revisit the question that I had with Bayer.

DR. MILNER: No, I just -- and the question again was either to Bayer or to the FDA, as to whether actual pathology of the surrounding tissue of removed implants was examined in both cases of suspected inflammation and where there's no suspected inflammation.

DR. IGLESIA: And, quite honestly, that question would maybe help address the de novo development of nickel allergy.

DR. FISHER: So just a quick response. Was pathology done? Yes. Pathology would have been done for the chronic and the subacute systemic -- oh, I'm sorry.

DR. MILNER: Josh Milner.

I'm talking about the patients.

DR. FISHER: Oh, patients. Right, I was -- okay.

DR. IGLESIA: So please introduce yourself again.

DR. ZAMPAGLIONE: Sure. Edio Zampaglione, Bayer.

Yeah. In the preclinical trials, the women who were pre-hysterectomized, they got Essure, and then there were sections that were done. Let me bring Dr. Mario Caturegli up here, who can explain and give some information on these. And we do have some slides also that will show this.

DR. CATUREGLI: Good afternoon. My name is Patrizio Caturegli. I am originally from Italy, as you can tell. I trained as endocrinologist, and then I trained as a pathologist at Johns Hopkins University, where I am an associate professor, and I am also the director of the Autoimmune Disease Research Center.

I reviewed the study that was published by Valle, about 51 patients that were predicted to go to hysterectomy and had the Essure implant device. So I reviewed those images. You're going to get the slide, but I reviewed the images, and the images show evidence of inflammation, which is what you would predict to see in a patient that received an implant.

So this slide shows an example. On the left side is a cross-section of a fallopian tube. You can see the lumen in the center line by the mucosa, and they are basically around the inflammatory cells that infiltrated the mucosa.

And then the middle section is an example of a woman that is -- the utero was sticking out 1 week after the implant. You can see that around the device there is an accumulation of inflammatory cells. This magnification is difficult to see, but the cells are

represented by -- mainly by polymorphonuclear cells. So it's an indication of acute inflammation.

And on the slide on the right you can see, about 3 months after the implantation, the acute inflammatory cells are gone, and what predominates the architecture is the position of collagen fiber, which is basically a scar. So it's a fibrotic reaction that is the attempt of the body to wall off and form a barrier around the device.

DR. MILNER: Josh Milner.

I guess the question was -- this is exactly what you would expect to happen when you implant it. The question was when they were removed for pathological reasons when inflammation was going on, compared to when they were removed not for pathological reasons.

DR. CATUREGLI: Yes, this is a very good question. We discussed it, and nobody has the data. If the data can be acquired, we'd love to look at those slides.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: My question is on FDA protocol. Can I ask that now?

DR. IGLESIA: Actually, can I ask one question about -- Bayer, about what you quoted or thought is your rare background rate of nickel allergy, for the reason not doing a screening for it? How did you define rare?

DR. ZAMPAGLIONE: So Edio Zampaglione.

Are you referring to from the original PMA and getting into the label?

DR. IGLESIA: Correct.

DR. ZAMPAGLIONE: We don't have that information now. We can try to look and

see if we can get it for you, and if we can, we will. But at this time we don't have it.

DR. IGLESIA: Sorry, Ms. Chauhan. Go ahead.

MS. CHAUHAN: No, that's okay. Cynthia Chauhan.

If approval is continued, does the FDA have the authority to have a company cease and desist any consumer advertising as part of the approval?

DR. FISHER: As part of the approval?

MS. CHAUHAN: Yeah. You know, you can keep this device --

DR. FISHER: So we would review -- right, we would --

MS. CHAUHAN: -- but not advertise directly to consumers. Can you do that?

DR. FISHER: So this was -- okay. So this was reviewed under a PMA, which is -- this was reviewed under a PMA. Oh, okay. Ms. Wolf will answer that question, from the Office of Compliance.

MS. WOLF: I'm Deborah Wolf. I'm regulatory counsel in CDRH's Office of Compliance, and I deal primarily with promotion and advertising issues.

The Agency doesn't have the authority to tell a company not to advertise, and we don't -- generally, we're very different from the Center for Drug's authority. If anybody is familiar with Drug's authority, Devices' authority is very different. We don't pre-review or review, as CDER does, simultaneously look at promotional launch of materials. So the only advertising authority that we have for restricted devices, which this is because it's a Class III device, is to require that advertising include a statement of the product's intended use and any relevant risk information that's related to that, to the use.

DR. IGLESIA: So we have about 15 more minutes left on this deliberation. I know

that Dr. Stubblefield had a question way back, if you still remember it. And I will also go around the table for anybody who has not spoken.

Dr. Stubblefield.

DR. STUBBLEFIELD: Phil Stubblefield.

This is a completely different topic. We were shown today, by more than one of the speakers from the public, copies of research forms that had been crossed out and new information put in, and we were also told that in some cases the investigators just filled out the forms for the patients and the patients didn't see them. Can someone speak to this?

DR. IGLESIA: The FDA and Bayer.

DR. FISHER: What's that?

DR. IGLESIA: The FDA and Bayer, for their pivotal trial.

DR. FISHER: Sure. So yes, I would like to point you to page 19 in the Executive Summary from FDA, and it says that "The FDA is aware of allegations from women who participated in the original Essure clinical trials that the feedback they provided about the comfort wearing the device was not recorded accurately by clinical staff." At the time of the issuance of the PMA, there are inspections that take place during that time. And I think the concluding statement there is that "These inspections audited data provided in support of the PMA, as well as sponsor activities during the studies, and did not report findings concerning the case report forms or patient comfort/satisfaction data submitted in support of the PMA."

Now, the one thing that I cannot do right now is comment, I can't acknowledge, I can't give updates on any compliance actions that might be under way.

DR. IGLESIA: May I ask Bayer to comment as well?

DR. FISHER: Sure.

DR. IGLESIA: Would you have additional comments? And state your name.

DR. ZAMPAGLIONE: Sure. Edio Zampaglione.

So, first of all, no one has alleged that anyone at Bayer has changed these records, okay? These allegations are part of a telephone interview from 2002 that was initially completed by a research assistant and then updated by the lead investigator. What was shown on the screen before was totally good clinical practice followed. Changes were made that were crossed out, initialed, and dated. And when you actually look at the entirety of the forms, you'll see some areas where there was a yes, adverse event, then crossed out to no. But if you look later on towards the end of it, you will see a no that was crossed out and then a yes put in. So we can only speculate, and I can't comment any further than that, but all I can say is good clinical practices were followed, all the rules were followed. It just seemed like things were being moved around a bit.

DR. YUSTEIN: Dr. Iglesia, Dr. Corrado wanted to add a couple of statements regarding that issue.

DR. IGLESIA: Please. Dr Corrado.

DR. CORRADO: So when FDA became aware of this issue at the time of the meeting we had with some patients who had had bad experiences with the product, we took it very seriously, and we looked into whether it was possible to audit all of the case report forms from the Phase II and pivotal studies, and we were told that these forms are not required to be maintained beyond a few years. So that was not possible for us to do. What we did do

is we were in the process of reviewing the -- a later IDE study for the transvaginal ultrasound protocol, and that study enrolled approximately 600 women. And as part of our review, when we became aware of this and saw the evidence that the patients brought us, we thought that we should do everything that we could to determine whether there was a pattern and whether similar events were happening in subsequent IDE studies and whether there was a pattern that this was happening across many women.

So I will tell you what we did, and that is that we asked the company to look at specific case report forms for that study on which adverse events were collected. There were Case Report Form 7, 8, 12, and 13, at which time information on adverse events was collected. Case Report Form 16 was a form that collected data on unscheduled visits or study contact. So we asked the company to identify where any -- on any of these case report forms someone reported pain or another adverse event and whether if on that case report form there was also information on comfort wearing the device, because we wanted to know if there was discordance between reporting of pain or an adverse event and, at the same day, excellent or very comfort wearing the device. And the company provided extensive records following an audit of all of those case report forms.

And what I will share with you, and I'm hoping it's okay with the company, is that it appears that there were approximately six cases of the approximately 500 or 600 patients where it was possible that there was a discordance. Although not having been there, we can't say that, you know, somebody intentionally misrepresented someone's level of comfort wearing the device. But, because of that very small number, six out of a very -- approximately 600 patients, we concluded that there was not a pattern of discordant

reporting. So that is how we handled that. Put it to the Panel to discuss.

DR. IGLESIA: Was that just one particular site where this was a problem or just --

DR. CORRADO: No.

DR. IGLESIA: Okay.

DR. CORRADO: No, no. So these were sporadic case report forms across multiple sites.

DR. IGLESIA: Yeah. Thank you very much.

Does that answer your question, Dr. Stubblefield?

DR. STUBBLEFIELD: I guess that's the best we could get.

DR. IGLESIA: I'm going to move down the line here.

Dr. Elser.

DR. ELSER: This is Dr. Denise Elser.

This is for either the FDA or for Bayer. In the reports coming in now through MDR, does there seem to be any geographic pattern? Are these clustered or all over the place?

DR. IGLESIA: Would you like to answer?

DR. YUSTEIN: Yeah, sorry. Ron Yustein from FDA.

In our analysis, we did not break it down by geographic location within the United States. Most of the reports are from within the United States. We also do get some reports outside -- from outside the United States, but most of them are U.S. But we don't have it broken down by geographic region. Sorry.

DR. IGLESIA: Bayer, would you like to respond as well?

DR. ZAMPAGLIONE: Sure. So Edio Zampaglione.

I'd like to call up Dr. Andrea Machlitt, our global pharmacovigilance lead for Essure.

DR. MACHLITT: Andrea Machlitt, Bayer HealthCare, Global Pharmacovigilance.

We do collect adverse event information from postmarketing sources worldwide, and we pay attention to the geographic location. Regarding Essure adverse event reporting from postmarketing, we have to state that the large majority of cases are reported from the United States. That can in part be explained by also over 60% of the devices having been sold in the United States, but it is also emphasized in postmarketing reporting in general.

If you would bring up Slide 1, please.

Our global safety database contains about 17,563 adverse event reports in total. So this is all cases regardless of the causality or of the source of information, and as you can see, United States accounts for about 15,000 of these reports. Other countries that present with a larger number of case reports are France, Netherlands, Spain. And that is also representative of the market share Essure has in other countries than the United States.

DR. IGLESIA: Thank you very much. We'll just go down the line.

Deb, do you have any questions? Dr. Myers?

DR. MYERS: Deb Myers.

A question about post-procedure time period. Probably this is directed to Bayer. It sounds like you have resources for physicians to call when they have a complicated patient and need some guidance. Are there patient hotlines or resources as well for patients who are having problems and need expertise?

DR. ZAMPAGLIONE: Edio Zampaglione.

Yes, there are. We have a dedicated phone number for patients, and there's also

one that could be used to call the medical information line. But there is a specific line that's dedicated for Essure that women can call.

DR. IGLESIA: Dr. Chappell, anything?

DR. CHAPPELL: No further comments or questions.

DR. IGLESIA: Thank you.

Dr. Coddington.

DR. CODDINGTON: One following up on Dr. Elser's comment. Do you have it divided, as far as the comments, by size of practice? In the other countries that were listed, it's very commonly done at the center, knowing where the expertise is. In the United States, there would be a greater chance that it might be done more in a private practice setting or whatever. There is a learning curve on anything. Is there a way to have this -- and probably Bayer might have it more than FDA -- where it would be broken down by practice size or by number of procedures done? We heard individuals stating about how many they had done.

DR. IGLESIA: So, for clarifying, you're trying to figure out whether or not there are outliers who have higher than expected complications rates based on technique, learning curve. I mean, Doctor, they did explain how there are modules and simulation models and then the proctoring of a minimum of five cases before actually implanting. But the question is, where is the due diligence on sort of the outliers who may have greater than expected complications?

DR. CODDINGTON: Right.

DR. ZAMPAGLIONE: Thank you. So Edio Zampaglione again. Excuse me one second.

So I just want to make sure I understand the question. So your questions pertain to are we looking at outliers to see those clinicians or offices who have had higher rates of adverse events?

(Off microphone response.)

DR. ZAMPAGLIONE: Okay. It's very difficult to track, and we're not able to. What we do track or are starting to look at a little bit more closely, really, is the replacements that are coming in for various reasons. And if we do see -- in the cut-up, it was around four or five replaced for bent tips, let's say. That could potentially indicate a technique issue where we then have our Essure specialists go and find out what's going on. Is there a need for retraining? Is there a need for a proctor to go in? Is there a need for anything else to be done to try to find out what is going on? So that's the best that we're doing right now.

DR. IGLESIA: Does that answer your question, Dr. Coddington?

DR. CODDINGTON: Not ideally, but it's an answer.

DR. IGLESIA: Grace Janik, do you have any questions? You might want to follow up on your fragmentation question from the first session.

DR. JANIK: I have thoughts about things. The fragmentation. Why I was concerned about that is removal, and the long-term consequences for patients are much more profound if it's gathered through the abdomen, if you can't remove it completely. And then I question, with removal in general, what type of resources are available to patients, of who's capable of removing, what kind of outcome they have, how can you direct patients, and how do you know what those outcomes will be? It seems like that's a very important source of information, is these people that are being removed both from a pathological

evaluation perspective, evaluating what symptoms brought them there and then their follow-up after. So what's done with this resource?

DR. IGLESIA: Would you like to take that question? I mean, you talk about the bent tips. And do you have a recommendation of who to go to for complicated removals?

DR. ZAMPAGLIONE: Sure. So Edio Zampaglione again.

Yeah, there is a physician locator on the website that a woman could put in her zip code and whatever radius she wants to or is willing to travel. We also again, with the toll-free number, between -- from patients or even if it's a physician who has an Essure patient and is not sure, they contact us. They contact us through our medical information group, and we have a network of consultants. These are very highly expert Essure physicians, a lot of experience with the placement, but not only with the placement, the management and even removals. So we do offer as much guidance and especially peer to peer.

I mean, that's the most important thing, is to have that peer-to-peer guidance. Each patient is going to be different. Each case is going to be different. Each removal is going to be different. So it's really us trying to facilitate a physician who has that question, to connect them with somebody with a tremendous amount of experience to help guide them through.

DR. JANIK: If you have experience with placement, that really doesn't mean you have experience with removal. It's a completely different skill set, isn't it?

DR. ZAMPAGLIONE: Correct.

(Applause.)

DR. JANIK: Oh, my name is Grace Janik.

So I question how you really vet those people and what kind of outcomes you see, and with this, what percentage of them are fragmenting when they are removed, and how much follow-up of those removal experiences do you have?

DR. ZAMPAGLIONE: Okay. So it's a very good comment because you're absolutely right; placing it does not mean you're an expert at removing it. And that is again a couple of things. Number one, the instructions for use recently was updated with some more guidance, some more information about removals. We are incorporating a little bit more removal information into our training programs to try to -- to cover this, to try to give as much guidance as possible.

The experts that we have, these are well known in the minimally invasive world. They just have a tremendous amount of experience. We consult with them all the time, we interact with them all the time, learning from them, getting guidance, getting advice. That's how we vet them through, and these are the ones that we are utilizing. In fact, Dr. Basinski is one of them and really again has -- this resource has been proven to be very invaluable for the physicians out there. And we're working towards more -- providing more information and training on removal. There was more to the question. It was about fragments. I apologize, I didn't get the whole thing.

DR. IGLESIA: Tracking of fragments.

DR. JANIK: When they are removed, what percentage have fragmentation? Is the path evaluated, and is any history evaluated with removals?

DR. ZAMPAGLIONE: Okay, let me bring up again Dr. Machlitt from our global pharmacovigilance group to help answer that question.

DR. MACHLITT: Andrea Machlitt with Bayer.

So, in preparation of this meeting, we attempted to analyze all the information we have on women who undergo surgical procedures subsequent to the Essure procedures, including salpingotomies, salpingectomies, hysterectomies, and hysteroscopies, and many of them are in relationship with removal. Even so, that is not always reported verbatim.

I have a slide. Excuse me. Can we bring up Slide No. 1, please? Regarding complications of the device removals, I have a slide here that lists the total number of events we could identify, and that is 1127 reports of subsequent surgery, as I described beforehand. And what you can see here on that slide is a breakdown of cases with reported removal complications, and that accounts for 4.8% of the cases, and 95.2% were reportedly without complications. And you can see here that fragmentation is among the possible complications. But we also found that sometimes it's reported that the removal procedure could not be completed or the physician was unable to locate a device. Other complications such as postoperative infection or even more severe outcomes like embolism due to the conducted hysterectomy are very rare.

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: Given what we've heard about migration and perforation, it seems like placement of these coils may be fundamental to that. Can someone just review for us what the actual proctoring is of these five or more than five cases that are done? Can you go into detail about -- are those five cases, where there's bilateral placement, consecutively or is this five cases -- can we hear the details about that? What effort has been made to -- you know, this started 13 years ago. Is it the same instruction and the same training that went

on 13 years ago that's going on today? Have you modified it over time?

DR. ZAMPAGLIONE: Okay. So Edio Zampaglione.

I think I understand your question. What you were asking again is how is the training done? Is one case truly one case or just one attempt? Is that what you were asking?

DR. SEIFER: Can you give us some detail about the -- I know they read the manual, they go through the course, the proctoring process --

DR. ZAMPAGLIONE: Sure, okay.

DR. SEIFER: -- and how you sign off on saying somebody knows how to do proper placement.

DR. ZAMPAGLIONE: Sure. So basically, again, as you had said, they go through the didactic, they get all the clinical information. They then do the simulator, whether it be the uterine model or the electronic simulator that very well simulates these cases. They then go on to live cases. That is done whether in the physician's office or an operating room by our Essure specialists. They are there to make sure the physician understands the appropriate steps following the delivery catheter, going to the specific markers on the delivery catheter, being able to release it appropriately, and that they have the proper amount of trailing coil, such as between three to eight is what is the ideal number of trailing coils that are left inside the uterus.

Though most of the time it is able to be done in one setting, sometimes it's not. If there's a tubal spasm going, that's really one of the major things to stop, do not keep trying to force. That's where you really increase the risk of perforation, but that is not considered

one case. If they have to go back and make a second attempt then and it's completed, that would be considered the one case. After that fifth case, then there's the sign-off case where again, if they're able to demonstrate that they know the procedure, they're able to place it properly or successful bilateral placement, they then get their certificate of completion.

DR. SEIFER: And that's pretty much the end of the training process. They're signed off, and then is there any other surveillance after that?

DR. ZAMPAGLIONE: The physicians themselves, no, they no longer followed a proctor intentionally. If they ask, if they say, you know, I would like another case to be supervised, that's where -- or if they even request another physician to come in, that's the proctor program that we have that is peer to peer. But once they get the sign-off case and they get their certificate of completion, they are done.

DR. IGLESIA: Thank you.

Ms. De Luca.

MS. DE LUCA: Looking at the other end of the spectrum, I live in a small community now, and it's a lot of poverty in our community, and unfortunately most of the people have no insurance, and if they can't go to the free clinic or the family clinic nearby, or the man that has the roving wagon that does free physicals, they're probably not going to seek anything. They're just going to stay at home and suffer because they just have no other options, and that's pretty much a large part of the deep southern population. So I'm just bringing that up. It's not always just Bayer's fault or the doctor's fault or following people. It's just a matter that people don't seem to have a choice, a path that they know that they

could follow.

DR. IGLESIA: Or lack of access.

Ms. Chauhan.

MS. CHAUHAN: This is a question for Bayer. You've been asked to specify geographical distribution of adverse events, and you always go to international, where the distribution shows that the United States has more. I would like to see if you have information on the distribution within the United States geographically.

Also I'd like to know, are all the devices manufactured in the same place and subject to uniform quality control? If they're not manufactured in the same place, have the problems come from one site more than others?

(Applause.)

DR. ZAMPAGLIONE: Okay, Edio Zampaglione.

So, breaking down geographically in the United States, that was your first question. That we do not have. I don't know if we're going to be able to get that. I mean, it's not something we'd be able to get right at this point in time.

But the other question -- I apologize. What was the second part of your question?

MS. CHAUHAN: The second part was about manufacturing sites. Are they all manufactured in the same place? Are they all subject to the same quality control? If they're not manufactured in the same place, have you noticed that one manufacturing site may have more problems than others?

DR. ZAMPAGLIONE: Got you. Great. I'd like to bring up Michael Reddick for that question. He's in our quality assurance department.

MR. REDDICK: Michael Reddick, with QA product technical complaints.

So all of the product that is being distributed is all manufactured in one facility, and so they're all contained within the same quality system. Does that answer your question? So there is one quality system that controls the entire process.

MS. CHAUHAN: Have you noticed any timeline difference in the ones that cause problems?

MR. REDDICK: Timeline difference. No. We do a very rigorous postmarket surveillance review of our data, and we have taken a look at that data to see if it correlates with any type of timeline or any certain lots, and we have not seen a correlation with that.

DR. IGLESIA: Dr. Gardner. And then I'll come back to this side. I think there were two questions here.

DR. GARDNER: Jim Gardner.

And this is a little bit of a piggyback on Cynthia's question. We talked about complaint rates in the U.S. and outside the U.S. We talked about the fact that you really can't use those well to establish actual rates. Having said that, probably a lot of us sit here and try to do the math in our head and understand, well, what might the rates be? Can you share with us again what are -- how many devices have been placed since the inception and how many of those have been in the U.S. and how many of those have been outside the U.S.?

(Applause.)

DR. ZAMPAGLIONE: So Edio Zampaglione.

Since approval, approximately 1 million units or kits have been distributed

worldwide. We are not able to track each individual patient or how it gets to, because of the distribution process that incurs. And this is just standard with these type of devices in the industry. Most of the sales are in the U.S., as I think Dr. Machlitt had shown. Essure is distributed in 23 different countries. The U.S. has the biggest portion of the sales or distribution. I don't have a percentage off hand at this point. I'm sorry, I just got it. It's 60% are in the United States. The other 40% are in the other 22 different countries worldwide.

DR. IGLESIA: Dr. Katz, did you have another question?

DR. KATZ: Two questions back on that question. So we're trying to understand the distribution of complications and adverse events, and we're trying to understand what the denominator is and the way we think about it, as well as the details of the provider. Now, does Bayer have -- you showed a chart in which you looked at the prevalence of AE reporting, and I think the number was something like 87% was in the states, and the other 13% were in about 20 countries. Can you take that chart and at least normalize each number by the sales to that country? Because the impression is that the incidence of these reports is much higher in the states and that, in fact, it may not be simply -- and I think one of the key questions is, is it because more devices are in the states, or is it the way the devices are being provided in the states?

DR. ZAMPAGLIONE: I'm going to bring up Dr. Machlitt to help with that one. Yeah, Dr. Machlitt.

DR. MACHLITT: Thank you. We can certainly break down the numbers of the per sales in a certain country, but let me point out one aspect, and that is we are talking about

postmarketing reporting, which is acknowledged to have a factor of underreporting. Typically that degree of underreporting is fluctuating. What we have seen in recent years is strong input from the side of the consumers with a lot of consumer reporting. We believe that the social media plays an important role in that aspect. So what we currently see is stimulated reporting, many reports that also date back to previous years, as you also heard today. And that all has an impact also on the distribution of the adverse events generally. When we try to understand the safety profile of a device, we look on the global data, and we currently base it on an estimated 1 million devices sold overall and the related number of women who are potentially exposed to the device.

DR. KATZ: And then part two. On quality control, what is the quality control?

(Applause.)

MR. REDDICK: Michael Reddick, with QA technical complaints.

So we have one quality system that governs the process from the very beginning to the very end. Our oversight of quality begins at our suppliers. We provide our suppliers with specifications that have to be met for the raw materials and subcomponents that we use. Once those materials get into our process, we have an incoming inspection process that there's defined procedures and things that we look for, things we inspect for.

Once we inspect those materials and they pass, they get into the production process. As with any device manufacturer, there are multiple steps in a manufacturing process. So with every one of those steps, we have very clearly defined and established work instructions, procedures, specifications that have to be met by the product at every single step. Once the product gets all the way through the process, there is a testing that occurs

at the end. So every production lot that's made, we pull samples from that lot. We do destructive testing on the samples. We do functional testing. After we confirm that the device works as intended, we then tear apart the device and test the individual components to make sure that those components meet our specifications. After all that testing is done, we then send the product to a sterilization process. After the sterilization process, we then do additional sampling from the same lot. So we sample again, and we do functional testing again. And then we do visual inspection throughout the entire process. So we feel that we have very, very good, tight controls over our manufacturing process to make sure that we get the best product out to our customers.

DR. KATZ: Some of that testing is, of course, going to be in accordance with standards organizations, like the materials that you receive, focusing upon the completed devices. Now, has any of that testing been created specifically for -- to be suited to the performance of Essure? Is there anything unique to the testing of the Essure device?

MR. REDDICK: We have a couple different types of testing that we do. Some of it is just like tension testing, making sure that bonds are to a certain strength, testing materials to make sure that they have the strength required. We do have a functional test that we've developed, which basically simulates the actual uterine cavity and how the device actually moves. And so we do have a functional test that we use, and we also have standard testing.

DR. KATZ: So that's a mechanical test simulating the in situ environment. Is there any testing done where you simulate the in vivo environment? It's like accelerated aging, but you take the final device and you look at it under those conditions to see what it's like at high temperature, for example, to look at what it's like months later, for example.

MR. REDDICK: That's not part of our normal production process.

DR. IGLESIA: Okay, I think we have two final questions before the break. Dr. Baird and Dr. Wills-Karp.

DR. BAIRD: Dr. Baird.

I wondered about the people who don't have success on the first time, and there has to be another trial to get a bilateral implant. And do you know how many of those -- how does that work? Do they have to pay double, then, or what happens with the costs? And who provides the extra? And can you estimate how many of your million implants that have gone out actual are not actually placed? And does that vary by country?

(Applause.)

DR. ZAMPAGLIONE: I'm sorry, I couldn't hear the second part of the question.

DR. BAIRD: And does that vary by country?

DR. ZAMPAGLIONE: Is it by country? Okay, there is no extra cost to the patient. Okay. So if there has to be a replacement, that's taken care of. Let me see who would have the other part of the question, that if we have -- do we have anything on the number, you know -- and you're talking postmarketing, of course, right? You're not talking from the clinical trials.

DR. BAIRD: Right.

DR. ZAMPAGLIONE: Correct.

DR. BAIRD: Correct.

DR. ZAMPAGLIONE: Yeah, we'd have to look into -- yeah, we'd have to look into that one because that's postmarketing information. Yeah. We have it for the clinical trials.

Would that be helpful?

DR. BAIRD: No, I'd really like it for postmarketing.

DR. ZAMPAGLIONE: Sure, sure. Yeah. We'll try to get that for you.

DR. IGLESIA: Okay. And then maybe before the next question session. Last question before the break.

Dr. Wills-Karp.

DR. WILLS-KARP: Marsha Wills-Karp.

In listening to the speakers this afternoon, it seemed like there were a lot of complaints of autoimmune-type responses. So I'm wondering if any family history of autoimmunity or any data was collected. You may not have known that a priori obviously in the clinical trials. But do you have any information suggesting also that perhaps that information should be collected at some point?

DR. ZAMPAGLIONE: Sure.

DR. IGLESIA: Right, somebody mentioned HLA type.

DR. ZAMPAGLIONE: So Edio Zampaglione again.

No. For the clinical trials, that information was not collected or asked ahead of time.

DR. IGLESIA: Okay, we will now take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any members inside or outside of the audience. We will resume at 5:42. Thank you.

(Off the record at 5:32 p.m.)

(On the record at 5:50 p.m.)

DR. IGLESIA: At this time let us focus our discussion on the FDA questions. Copies of

the questions are in our folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the Executive Summary, the presentations we heard today, and the expertise around the table. With this said, I would ask each Panel member to identify him or herself each time he or she speaks to facilitate transcription.

FDA, please read the first question.

MS. BLYSKUN: This is Elaine Blyskun, Branch Chief for OB/GYN devices at FDA.

Based on available information, the following events have been reported to occur in association with use of the Essure device (Note: This list is not intended to be a complete listing of all adverse events reported to have occurred in association with Essure):

a. Procedural pain that is persistent, or new pain that arises at a later point
b. Perforation of the uterus and/or fallopian tubes by the Essure insert
c. Intra-abdominal or pelvic device migration
d. Post-implantation bleeding irregularities
e. Metal (nickel, nitinol) allergy or hypersensitivity reaction
f. Pregnancy (e.g., ectopic pregnancy)
g. Other

Please discuss each item and comment on the following:

a. The degree of association of the item with use of the Essure device
b. The reasons for this conclusion
c. The level of your concern for the item, if any, and the level of evidence to support the concern

DR. IGLESIA: Okay, I'd like to lead off the discussion actually with our Patient Representative and to see if you have any other concerns or any other information and your general impression on this particular question.

MS. DE LUCA: All right. Jo-Ellen De Luca, Patient Representative.

I feel that the answer, from the patient point of view, is still out there. I think that this has been a great opportunity to find some possible answers, but I think there's still some great unknown. I lead a very large support group, and I know a lot of patients will be, knowing I'm here today, but will be concerned around the country, knowing -- looking for answers when this comes out. And I think that we have plenty of patients that have been here that don't have their questions answered, and I feel that will continue.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: In thinking about these, I've been thinking about the large number -- oh, Cynthia Chauhan. I'm sorry.

DR. IGLESIA: No problem.

MS. CHAUHAN: Cynthia Chauhan, Consumer Rep.

In thinking about these, I've been thinking about the large number of women who have identified themselves as having problems and a kind of consistency of the problems. It made me wonder if there's a role for genomic variants testing in this, where I think a real issue if this drug -- I'm sorry -- if this device stays on the market is, going forward, how do you find people for whom this is an appropriate device, who will not be subject to these? And I think, looking at this cohort that's existing and planning from that and considering genomic variants may be useful.

DR. IGLESIA: Thank you very much.

Would anyone like to lead off the discussion regarding these listed complications and the degree of association of the Essure device? Let's start with pain.

Dr. Stubblefield.

DR. STUBBLEFIELD: Procedural pain that is persistent seems to me to be highly likely to be associated with the device. Pain, a new pain, less clearly associated. Could be, could be something else. So many different structures that can cause pain in the pelvis.

DR. IGLESIA: May I ask, is that -- you're saying that it's going to persist because you're off, you've changed the modality of contraception from something that may have also addressed the pain, i.e., continuous birth control pills, to something else or -- or what led you to that conclusion?

DR. STUBBLEFIELD: Well, I think you're absolutely right. I wasn't actually thinking of that at the time.

DR. IGLESIA: Oh.

DR. STUBBLEFIELD: I was thinking of it as related to the surgery --

DR. IGLESIA: Okay.

DR. STUBBLEFIELD: -- or to the procedure. But that's an important consideration --

DR. IGLESIA: Okay.

DR. STUBBLEFIELD: -- as we've already discussed. Abandoning the previous hormonal contraception.

DR. IGLESIA: Dr. Coddington, then Dr. Janik.

DR. CODDINGTON: Dr. Charles Coddington.

I agree with Phil, and I think the practical point is that probably 1-2% of the fallopian tubes are not just straight shots in the sense that they're very tortuous, and the development of the female genital tract has aspects of that, as a woman develops her cervix, also may be very tortuous. So I think the point is, is that there are going to be some anatomic variations, so it would not be inappropriate for there to be some implant that would be more painful or certainly less comfortable. There will be some, if you will, that it will just drop right in and there won't be a problem at all.

So I think that just kind of looking at separating potentially these two things out where there is procedural pain, and then we can talk about how to evaluate for that and that sort of thing from the other in the sense that, yeah, the device could migrate out the tube causing a similar type of pain, true, but I think one of the things that I think has broken down here, no pun intended, is the fact that the physician/patient bond has been broken in the sense that many of the young ladies we heard from today did not have the confidence and good interaction with their physician, that they could come back with a problem and get a reasonable evaluation and answer. And I think that is a concern that I have of some of the things that I've heard, so I think we need to try and figure things out as close to the point of service as we can so that people do not suffer for a month or whatever before something is done and evaluation carried out.

DR. IGLESIA: Dr. Janik. Thank you.

DR. JANIK: Grace Janik.

I look at the pain as different, too. If you look at some of the literature, most of the pain that's procedural pain is resolved by 99% by 7 days, so if you have pain that started at

the procedure and it's still persistent at a week, you probably have a problem and maybe you should intervene and it shouldn't be --

(Applause.)

DR. JANIK: -- many, many months to years before it's addressed. So I think there's an opportunity for early intervention analysis of a placement issue.

And then there's the second, of pain that develops later and -- which could (1) coming off of OCPs or whatever was the previous birth control method, or is there delayed pain that could be device related, and I think that the only way to really know that is more study. I don't think you can really answer that with the data that we have available. But I do wonder how much support that physicians and patients have gotten for that early phase when they call and what should I do, and maybe early intervention before we risk bowel obstruction as the thing has migrated through should be a change in protocol thought rather than wait it out and see what happens.

DR. IGLESIA: So your level of concern seems rather high?

DR. JANIK: I think it's high. It reminds me of endometriosis --

DR. IGLESIA: Um-hum.

DR. JANIK: -- patients which wait 7-8 years before they have a diagnosis and three or four surgeries before it's corrected.

DR. IGLESIA: Um-hum.

DR. JANIK: So it has that same feel to it.

DR. IGLESIA: Um-hum. And so -- and maybe you might recommend some imaging earlier rather than just general --

DR. JANIK: I would suggest imaging if, you know, if you're not resolved definitely by a week. You do some imaging, 3-D ultrasound, you probably can see if you have migration, perforation. You can see if you have a problem early.

DR. IGLESIA: Other discussion on this topic of pain?

Dr. Myers.

DR. MYERS: One thought as we've been listening today is some sort of -- like some sort of protocol change. Maybe there's a post-procedure ultrasound that's done to confirm placement in the tube, is it already perfed through the tube, you know, something a little bit more timely than 3 months --

DR. JANIK: And I think that would be wonderful, too, if you have problems at a week or ideal would be if you do the procedure and you do 3-D ultrasound --

DR. MYERS: Right then and there.

DR. JANIK: -- right after the procedure, you're done. It's like part of the procedural package.

DR. MYERS: Exactly, yes.

DR. IGLESIA: Other comments on pain? Yes, and then we'll move on.

MS. CHAUHAN: Cynthia Chauhan.

My question is to Dr. Coddington and Dr. -- I'm sorry, I can't - - Janik. Would there be any usefulness, given your comments about the physiology and your comments about the length of pain, to pre-procedural imaging to check the tubes to see that they can handle this?

DR. JANIK: Grace Janik.

No, because you can't see it. It's all just -- and it's all soft tissue, it's all angled, it's all how you manipulate things, and there's not imaging that would really help you with that.

DR. IGLESIA: I actually do think that this is a nice -- this conversation is a nice segue to 1b and 1c, you know, because of the anatomic variations and the possibility of whether or not, when you put it there initially, is it in the right spot for a perforation and/or is it in the right spot and then -- or is it out of the right spot and has already migrated. And so that then leads to this question of intraoperative evaluation or early procedural intervention for imaging. Is there discussion on that?

DR. JANIK: I agree with everything you said. Grace Janik.

So I think immediate ultrasound or very early ultrasound -- complications to -- for documentation.

DR. IGLESIA: Yeah.

DR. JANIK: Rather than waiting to discover.

DR. IGLESIA: Rather than waiting up to 3 months for just occlusion because you're --

DR. JANIK: Because there's two things you want. You want, one is --

DR. IGLESIA: Confirmatory.

DR. JANIK: -- placement damage, and then the second is occlusion. It's two different topics. So separating the two answers could be beneficial for the patient.

DR. IGLESIA: Quite frankly, I do think that there is an issue, it seems maybe 2-3%, I'm trying to figure that out, where it's not working, whether it be tubal spasm, the anatomical variant of the tube. I'm saying if this is not going smoothly, we need a Plan B. I mean, the patients need to be saying, okay, we can't get this in. You want permanent sterilization, we

have permission to go ahead and proceed with the tubal ligation or whatever you end up deciding to do. I'm not necessarily sure that that conversation is happening.

Dr. Coddington.

DR. CODDINGTON: I think a lot of them, there were a few young ladies that had had the procedure done under anesthesia, and that would be a very reasonable Plan B. But many of them have them done in an office with maybe a paracervical, if that.

DR. IGLESIA: Yeah.

DR. CODDINGTON: And so I don't know if you could reasonably do that, but it's a great thought.

DR. IGLESIA: Oh, I'm not saying on the same day, but you'll say --

DR. CODDINGTON: Oh, yeah. Yeah.

DR. IGLESIA: -- oh, we're aborting this, this is not going smoothly. We, you know, need to schedule it.

DR. CODDINGTON: Right, yeah.

DR. IGLESIA: Absolutely.

Dr. Wills-Karp.

DR. WILLS-KARP: So Marsha Wills-Karp.

I agree. I also think that if you decided early on that it wasn't working for some reason for that individual, removal at that time would be a lot less complicated --

DR. IGLESIA: Yeah.

DR. WILLS-KARP: -- than waiting until it's embedded and causing other problems.

DR. IGLESIA: Yeah. It didn't go in smoothly, you have more coils, you know, no more

coils are left, and so you know that this thing is probably in too deep or there's too many coils and the whole thing, so it's going to expose because you're not in far enough. Abort. Abort and go get a Plan B.

Dr. Elser.

DR. ELSER: Denise Elser.

Several of the articles in the literature comment on that perforations and complications were more likely when they went back and asked the clinicians if they had difficulty with the procedure. So, again, there may be more guidance on if it's not going smoothly, you can wait for spasms, spasms should alleve, and then it goes in smoothly again. But if you're still putting pressure, putting pressure, and the device does not go in the tube smoothly, maybe -- you know, we don't want to force it in, and there could be stronger guidelines.

DR. IGLESIA: Is that good discussion? I think we can move on to the bleeding irregularities, then. I will summarize, so we'll have more time, opportunity for discussion. And I know 1e is going to be one that's going to require probably a longer discussion. But the post-implantation bleeding irregularities, would someone like to lead this off?

Denise.

DR. ELSER: Well, I think this one is actually --

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

I think this one's actually hardest -- because unless we know how many women came off of hormonal contraception at the time of their Essure, and are they developing bleeding

abnormalities related somehow to the implant, or is it their own physiology that they are having bleeding abnormalities because of their age, their hormonal status. And I think we heard some comments, too, about people developing pain and found to have adenomyosis, endometriosis, and we can't comment if that's device related at all because that's a common finding in women who are not on hormone contraception.

DR. IGLESIA: Other questions, I mean comments on this, for the bleeding?

(No response.)

DR. IGLESIA: Okay.

Dr. Stubblefield.

DR. STUBBLEFIELD: On that question, I think that I understood, from reading the presentations, that part of the time the bleeding could be associated with perforation, and if that's the case, then maybe bleeding warrants at least an ultrasound to look for that and not just assume that's just endometrium.

DR. IGLESIA: That's a good point. Maybe one of the early intervention protocol to add that to the list, the checklist.

Dr. Coddington.

DR. CODDINGTON: I think in -- I mean, your point is well taken. In looking at this, we deal with abnormal uterine bleeding. And if you've increased the menstrual flow, then we kick over into a paradigm of working out the bleeding. I mean, heaven forbid she could have a polyp or other things like that that are intervening, or a myoma. All of those things are possible. They could -- you know, I can't necessarily relate them to the device in that sense, but what I'm saying is, is that we then address the problem of the bleeding and go

about that aspect so --

DR. IGLESIA: And clearly there were some case reports about pretty significant infections and abscesses and endometritis, and I think, you know, developing a uterine infection is also in there and is a cause for bleeding.

So let's tackle 1e, on the nickel allergy. I think we might start with Dr. Wills-Karp or Dr. Milner on this. Is that okay?

DR. WILLS-KARP: Yes. Well, first of all, I think we need more data, and I don't think, in the literature, that there's sufficient data to predict how nickel exposure in the reproductive organs, actually, how you respond to them. And is that different than skin or other sites? So I think we definitely need to understand that better. But I think in the context of the study, it would be worth collecting information about nickel sensitivity in people who have these devices and see if that is, with the larger sample size now, to see if it is connected with some of the symptoms. It may or may not be, but it seems like it's worth pursuing. I think on the same -- and I'm going to group it in here with the sensitivity because I think there may be some other altered immune phenotypes associated, and this -- hypersensitivity in general. It may not be to nickel alone, it could be to other aspects of the device or just the foreign body response by itself. So also to clear up --

DR. IGLESIA: Can I ask about your degree -- your thoughts on the degree of association of that with Essure and your level of concern? Just in terms of do you think that that would be an absolute contraindication or relative contraindication even right now as a recommendation?

DR. WILLS-KARP: Well, I agree with Peter, who I had also found that they had had

that as a contraindication early on and seem to have been lost somewhere along the way. I think it would be worth including at this point, but more data would probably be good because it may not be simply nickel; there may be some other aspects that need to be explored. I wouldn't want to just say it was nickel and then it would be something broader than that.

DR. IGLESIA: Dr. --

DR. SCHALOCK: I think --

DR. IGLESIA: Your name.

DR. SCHALOCK: Sorry. Peter Schalock.

If we want more data, we need to find what we're looking for, assuming a Type IV allergy, a delayed hypersensitivity. So, first of all, we need to define what test we're going to do to define what this allergy is, so we need to decide are we going to be doing a patch test for this, which, in general, even though it's not a perfect test and certainly data has shown it's not conclusive, does it predict anything? But at least it gives us some data: Is the patient nickel allergic or not?

The other option, which I think was brought up, I forget whose question it was, is there a blood test? There is a blood test that's available through, I believe it's Orthopedic Analysis, as well as some other companies out there, which is not FDA approved and not standardized, called the lymphocyte transformation test. Or the MELISA is, I think, a little variant of that. I would be a little hesitant to recommend something until it is a little bit more standardized and approved, but that test is out there, and some people believe that it's useful. So maybe that's something that needs to be explored, is doing a simple blood

test going to be enough to give us nickel data or -- as well as the other stainless steel components.

And my concern on this, I just feel like there's a disconnect between the number of women who are nickel allergic versus the information from the study, the Zurawin study, where they found essentially nobody had nickel problems, just -- I don't know. I just feel like if there's no data, that's -- I don't necessarily say the study is wrong, but on the other hand we don't have data, we don't know who is allergic, are they allergic, how often is it relevant. And maybe with a big enough sample size, we can actually do statistical analysis and figure out maybe there is a link. So I would be in favor of collecting this data somehow.

DR. IGLESIA: Dr. Milner.

DR. MILNER: So I think, first of all, we need to sort of separate out what we're talking about, as was discussed with Dr. Hamilton, and it's more likely that it's -- quite likely that it's more than one hypersensitivity. Whether it's a Type I and a Type IV, it's probably even something else. And, in particular, as it relates -- and with respect to the numbers that are coming up, being nickel sensitized and having a reaction are going to be two very different things. And then developing nickel sensitization once it's embedded are also separate things, and I think we've been confusing all three of those.

DR. IGLESIA: Right.

(Applause.)

DR. MILNER: So a point that I think is sort of bringing together what a lot of folks have mentioned during the public comment with respect to this auto-immune constellation or inflammatory constellation, so point No. 1 on that is, is that it would be great if we could

actually capture the inflammation, which is why I was so focused on what the biopsies of these specimens from people who had it removed -- and we've captured everything.

We know whether they've resolved, we know what they've been complaining about when they did, so getting a biopsy and looking to see what's going on seems to be an extraordinarily obvious thing to do to really get a sense of is there inflammation, because you can point to that, you can see it, and if it correlates with the complaint, then you have a pretty good sense that there's something that's happening, we don't know what, but something is happening.

Another point, though, that I think is important to make is that the constellation that a lot of folks have described, and in particular the downward slope of one thing and the next thing and the next thing and the next thing. So we actually -- it's important just to point out that especially in allergy, where we get brought lots of stuff where people don't know what's going on, we actually see that in many, many different scenarios well before Essure ever existed and well before -- in a variety of different settings.

Very often it is a major event. It could be trauma, it could be stress, it could be surgery or anything like that, and very often we see patients come in after such an event and begin to develop a series of complaints very, very similar to those which were brought up here. I have to be very clear. That doesn't mean that the response to this device is not one of the ways that this happens directly related to the device and not directly related to a trauma, but it just has to be pointed out that in addition to that, if -- to the extent that there is a direct correlation there, there does exist, even with autoimmune phenomenon, the emergence of antibodies, the emergence of specific complaints, and also in terms of

non-directly measurable things, which are unfortunately put together as functional complaints like bellyaches with no pathology or headaches with no pathology. Those are often unfortunately all thrown together, but they are very often seen in an allergy setting where it's completely unclear where it's coming from. And I just think it's important that it be out there that that's there, but not to sit and blame that possible thing which very often people say it's in your head, not to ever dare to do a thing like that, but just to be aware that it exists in both places.

(Applause.)

DR. IGLESIA: Okay. We'll go down the line, one, two, three. Sorry.

DR. CHAPPELL: Rick Chappell.

I would like to expand upon Dr. Wills-Karp's and Dr. Schalock's comments. More specifically, they asked that we get more information about allergies or sensitivities not only to nickel, but also perhaps stainless steel. And there's a third component, which is PET or its trace contaminants, which may well have undesirable inflammatory responses, because as far as I could tell, and I'm not the expert in this, but from reading Bayer's own material, it has a desirable inflammatory response, and that's how it implants. If it doesn't have an inflammatory response, it won't be effective. And therefore -- well, so that's a good -- it's intentional, right? And these patients should all know this if they were educated. But then it could perhaps not stop at the desirable level and keep going.

(Applause.)

DR. IGLESIA: Dr. Coddington.

DR. CODDINGTON: That was exactly what I was going to say, is not forget the PET, I

mean, because that --

DR. IGLESIA: And Dr. Seifer.

DR. SEIFER: David Seifer.

So this issue about the systemic reaction to mercury is just one example of many issues that we're concerned about in terms of collecting more data. Even the numerator/denominator incidents of these complications, pregnancy, blah, blah, blah, and what's been suggested by more than one person from the floor is the idea of a registry going forward so we can have an accurate assessment of the frequency of what's going on, whether it be this reaction or the other five or six issues that we're discussing.

DR. IGLESIA: Great. I think we have had a good discussion on the hypersensitivity/allergy. I'd like to move on to the pregnancy, if that's okay, issue and would anyone like to lead that discussion? I know that some Panel members talked about CREST 2.0 and -- Grace.

DR. JANIK: Grace Janik.

So it seems like the data when -- uses -- with follow-up at 3 months is done correctly is really pretty good. So I think that's the positive side. But it's disheartening that there's a disconnect between placing the device and follow-up for the 3-month evaluation, and especially that finances and insurance is part of the holdup. I feel like if you don't have the second part cleared, you shouldn't do the first part. They should be linked.

(Applause.)

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: So if they're going to be linked, then they should be -- it should be

committed to, to begin with, so they should be financing this whole up front so that it's part of the procedure and it's almost guaranteed that it happens.

DR. IGLESIA: Yeah, I think that the actual economic financing and stuff is probably beyond the scope of this particular group; however, the concept of the bundling of the whole method as one procedure, I understand.

Dr. Elser, Dr. Coddington.

DR. ELSER: Denise Elser.

Just for practically for part of the problem, because people are not the clinicians doing this, may not understand some of the implications of that. If the procedure is done in a surgery center and the surgery center accepts public aid because Essure is public aid, pays okay at that surgery center, but that they don't do HSGs there. And so then some places the HSG is done by a radiologist, some places it's done by the gynecologist and radiologist together, but now you're in another facility with another clinician charging, and so it's very complicated to make it a bundled payment if it's not the same facility.

DR. IGLESIA: Good point.

Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

One of the things is we might want to hold on that because, as I understand, there's a study coming up with ultrasound, and I think that that might be something that would be in the hand of the gynecologist and a bundling type of process could take place. So, like you say, we can't control the financial dynamics, but I think they're going to -- we'll have some information here relatively soon, I think. I don't know --

DR. JANIK: But I don't think it's responsible to put it in if you don't have that second part. And if it's not all worked out, I just feel like that should be a "no" barrier to going forward. You just can't offer it if you can't work it out at your system.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I think the bundling is really important, and I think a third component of the bundling should be skill in removing the device. I don't think people --

(Applause.)

MS. CHAUHAN: I think skill in removing should be on the same level of importance as skill in placing, given the problems we've seen.

(Applause.)

DR. JANIK: Can I comment?

DR. IGLESIA: I do think that physician training is Question No. 2, but thank you for that comment.

DR. JANIK: Grace Janik. I just want to comment.

The skill to remove is so different and such a higher level that I don't think you necessarily have to be the same person, but you have to access, you have to have a plan of where in your system they're going to go. It doesn't have to be the same person, but --

DR. IGLESIA: Yeah, I agree.

DR. JANIK: -- it shouldn't be a mystery of now what are we going to do.

MS. CHAUHAN: It's the bundling that matters, yes.

DR. IGLESIA: Dr. Elser, then Dr. Stubblefield.

DR. ELSER: Denise Elser.

So, once again, part of that is the way our payer system works currently that makes it a problem so that -- you know, I'm in Chicago, so let's say a lady has an Essure done at her doctor's office or a clinic in southern Indiana and they know that I may be the closest expert that knows how to remove it. I'm out of pocket because I'm not in her insurance plan. That's a huge barrier. So they might know where to send them. It doesn't make it doable for the patient financially.

DR. IGLESIA: Dr. Stubblefield.

MS. CHAUHAN: May I just respond?

DR. IGLESIA: Sure.

MS. CHAUHAN: Cynthia Chauhan.

It's my understanding we can't consider finances as part of our deliberations, but in the interest of good patient care, I think if you do not have access to someone who can remove successfully, you should not be implanting.

(Applause.)

DR. IGLESIA: Dr. Stubblefield.

DR. STUBBLEFIELD: Stubblefield.

While we're on the topic of the removals, I was really quite amazed to see that so often they are hysterectomies, and it sounds like often hysterectomies and bilateral salpingo-oophorectomies were being done, which is kind of like swatting flies with a cannon. Why do we need to do that? I don't know. Maybe part of the time there is other pathology, and it certainly makes sense if the patient wants to, but the amount of expense

and the amount of risk of doing a total hysterectomy as opposed to a laparoscopy or mini-lap removal with a linear incision, just no comparison.

DR. IGLESIA: All right. And I think some of this is also going to be in one of the questions about the removal. So is there any other discussion for Question 1? And we have the letter (g) as well to consider, if there is any other. I don't want to sort of limit the discussion to (a) to (f).

Dr. Myers.

DR. MYERS: Deb Myers.

Going back to the hypersensitivity events, what is -- and this might get answered later, but what is the current language in the patient insert? You know, is there some language in there that -- or could be added, you know, that this is a possibility, that some hypersensitivity might occur for the patients? In patient info.

DR. IGLESIA: I guess I would have to ask Dr. Fisher about --

DR. MYERS: I don't know. I'm just asking. If it isn't, is that something that we should consider recommending?

DR. IGLESIA: Dr. Milner, while waiting for that question, do you have a comment?

DR. MILNER: I'm not sure how you're going to be able to answer that because since the criteria were not laid out as to what the hypersensitivity is, it couldn't have been captured properly, so how could we answer that in -- the labeling, whatever it says right now, couldn't reflect what's actually being -- what's not captured.

DR. IGLESIA: Well -- you have another? Great.

DR. ELSER: This is not related to autoimmune. Denise Elser.

But while they're looking for the answer, I just want to point out also, yes, getting sterilized is an elective procedure. We always want to weigh the risk and the benefit. But pregnancy is dangerous. Pregnancy is dangerous, and ACOG has recently supported that hormonal contraception should be available over the counter because we felt it was -- or ACOG felt it was safer to let women go to the store and decide to take OCPs without a doctor visit than to be pregnant overall. So we want to just remember that, that yes, having a laparoscopic tubal ligation is not without complications as well, and patients get chronic pain after pelvic surgery, they get abscesses, they can become disabled also. So I just want to remember the context at which we're looking at this.

DR. IGLESIA: Great.

Dr. Yustein.

DR. YUSTEIN: So, in response to Dr. Myers' question, the current patient labeling brochure has the following statements: "The Essure insert is made of materials that include a nickel-titanium alloy. Once placed inside the body, small amounts of nickel are released from the inserts. Patients who are allergic to nickel may have an allergic reaction to the inserts. Symptoms include rash, itching, and hives."

DR. IGLESIA: So it's there as a potential known risk. Okay.

DR. YUSTEIN: And hold on, there's one more.

DR. IGLESIA: Oh. There's more.

DR. YUSTEIN: There's a section in there that says "You should speak to your doctor if," and it has a couple of bullets. One of the bullets says, "You have or think you may have a nickel allergy."

DR. IGLESIA: Dr. Milner.

DR. MILNER: So, again, that just -- that would then narrow it down to nickel when it could be from any number of sources.

DR. IGLESIA: Right.

DR. MILNER: And that's going to miss who knows what by doing that.

DR. IGLESIA: Good point.

DR. MILNER: So, again, when you just talk about hyper-sensitivities, that's any hypersensitivity, and if you narrow it to nickel, then that's going to be misleading.

DR. IGLESIA: We don't know what we don't know.

Dr. Seifer.

DR. SEIFER: I was just going to beg the question about the symptoms that were, I've heard about today, go way beyond that cutaneous reaction, and so I'd like to beg the question if it should be a little more --

DR. IGLESIA: Whole autoimmune?

DR. SEIFER: -- explicit.

DR. IGLESIA: Yeah.

DR. SEIFER: Yeah.

DR. IGLESIA: Okay. Let me see if I can try and summarize, unless there's anyone who has any parting comments on this.

Dr. Chappell.

DR. CHAPPELL: Chappell, right.

DR. IGLESIA: Yeah.

DR. CHAPPELL: Rick Chappell.

I do have a parting comment. Because we are not asked, as part of Question 1 or any other question, to provide FDA with advice under general strategy, but the situation we find ourselves in today absolutely demands it because postmarketing studies behind huge clinical trials, I'd say that postmarketing studies are especially good for detecting rare outcomes. A clinical trial even with a couple of thousand could not detect some rare outcomes. But as Dr. Juran commented today, she showed that many of the medical issues faced by the patients we heard from, as severe as they are, are very common in the general population, pain, et cetera.

And so we find ourselves in a situation, 13 years after this device was approved by the FDA, of asking ourselves about pain and bleeding irregularities and other very common outcomes. And we are doing so because this was approved on the basis of a so-called pivotal trial which was not randomized, not controlled; it was single armed. And I say so-called dismissively because I don't see how a pivotal trial can be a non-randomized, uncontrolled trial. Therefore, I recognize the logistical difficulties, the expense, but therefore, I strongly urge the FDA to abide by its own statement, which it made in 1967, that the gold standard is a randomized clinical trial.

(Applause.)

DR. IGLESIA: I think we can probably address that as well with Question No. 2.

So, to summarize, with regard to the assessment of clinical events, procedural pain, perforation, intra-abdominal device migration, there seems to be a problem for which we have some concern. And the concerns relate to the fact that we need more guidance for

practitioners who are doing this to be able to identify earlier, most early on before long-term complications occur, that we could have a problem. That could be done intraoperatively by assessment of intraoperative imaging to see exactly where these devices are located to mitigate the risk for accidental perforation or migration someplace else.

Or if the symptom of pain persists outside the typical, what one would feel is the typical time period of which one would have the usual procedural related pain, i.e., 7 days or whatever, then an early intervention analysis should take place. Same thing with regard to the development of bleeding and other, maybe unrelated to whether or not a different kind of contraception had been previously used. But if there are signals, then we need some type of protocol to be able to identify that early.

Does that summarize for those three?

(No audible response.)

DR. IGLESIA: With regard to the post-implantation bleeding abnormalities, the range is all over the place because the differential diagnosis for abnormal uterine bleeding is quite large, and there may be other causes that are unmasked because you've stopped other forms of contraception or you may have developed new reasons, i.e., polyp formation or an infection as a cause for bleeding. Again, some type of post-procedural protocol to be able to evaluate that earlier on would be helpful.

With regard to metal, nickel, PET or other -- stainless steel or other allergy or hypersensitivity reaction, this is a pretty significantly high level of concern, and we seem to have only scratched the surface in identifying nickel as a potential problem if someone has already a nickel hypersensitivity. But what we need is more data that's related to testing

pre-implantation, if at all possible, to include patch testing, blood test including -- I'm sorry, the lymphocyte MELISA test, and what I think makes a lot of sense is anything that is actually removed to have post-implantation biopsy/analysis/histopathology and analysis of the actual pathology of the device in relationship to the surrounding tissues to see if that is related to a hypersensitive reaction, inflammation or whatnot.

That being said, we also talked about the need for registries for identification of things that are rare, potentially such as this, a hypersensitivity to something, and even a registry for the common. There seems to be some general consensus that postmarket surveillance with some type of registry would be helpful.

Does that summarize that for that? For the allergy hypersensitivity issue.

Finally, with regard to -- no. Okay. Finally, with regard to pregnancy, seems to be that we need long-term data with good follow-up and some comparator data, I mean, what Dr. Chappell was referring to in terms of a randomized clinical trial, some type of comparator. You know, randomized clinical trials are obviously the gold standard. We had -- since I only saw that there was one study that had a comparator with the gold standard laparoscopic procedure, any type of prospective cohort with the comparator which can be done within the auspices of a registry might be feasible as well.

Now I brought up something else, I probably opened up another can. But go ahead, Dr. Chappell.

DR. CHAPPELL: Thanks. I want to clarify that, alas, I was not recommending a randomized clinical trial right now, in the present instance, because the window of opportunity may well have passed and it would take too long. But I am pointing out that it

was a mistake not to have done so and that I request the FDA not repeat it for future devices.

DR. IGLESIA: Dr. Coddington. I didn't do a great job on that last one.

DR. CODDINGTON: No, I think you did fine. Because I think the reality is, is that to be honest, we don't know what we don't know. And, you know, when you do randomized trials, you have to be able to figure out what you're trying to randomize from what. And we have two expert allergists, and we're not sure where we are there. I mean, I think we need to kind of better define that, if we get a specimen that we can look at the pathology and find different types of reactions --

DR. IGLESIA: Yeah.

DR. CODDINGTON: -- and different types of cells in the histopathology. That's going to make a world of difference. So I think more of a registry is a good place to go.

DR. IGLESIA: Dr. Fisher and Dr. Yustein, is this adequate? Do you have other questions?

DR. JANIK: Sorry.

DR. IGLESIA: Oh, no. No.

DR. JANIK: Dr. Janik. One comment.

You forgot in the pregnancy summary is to have the follow-up study linked with the procedure.

DR. IGLESIA: Correct. Thank you.

DR. YUSTEIN: Dr. Iglesia, we specifically let (g) on there to make sure that we weren't leading the Panel into just a focused discussion of things that we thought we had

focused on. Were there other topics? Because here's the chance to bring those up --

DR. IGLESIA: Okay.

DR. YUSTEIN: -- because the other questions are kind of follow-ons to this question, so if there are other concerns, you heard a lot of different adverse event types discussed today by all the presenters, not just the external presenters, but FDA and the manufacturer as well. Are there other issues of particular concern that we might be looking to in future questions to address in terms of mitigation strategies, labeling changes, et cetera? I just want to make sure that we have that.

DR. IGLESIA: I guess to summarize that some people were talking about the availability of other contraception, making sure that women were informed about options for other contraception, and the bundling. This is a method, that the procedure itself should be linked to the necessary 3-month post-procedural follow-up for, you know, complete analysis. And also if there is a complication that's necessitating a removal, that that also be linked, that, you know, if you can't put it in, you can't -- if you can't take it out, you shouldn't be able to put it in. I think we had those kinds of discussions.

DR. YUSTEIN: Right, I understand. I just want to make sure, like, you heard people talk about, you know, infection. You heard people talk about headache, fatigue, weight gain. There are other adverse events that were mentioned today that we didn't include on that list, but we just want to make sure that there's no other major type of event that people are concerned about.

DR. IGLESIA: Dr. Milner, then Dr. Elser.

DR. MILNER: You can even add -- you should also probably add cancer since -- it may

be more rare but obviously looms quite large to anybody who would be thinking about that. I think the issue that we're all sort of struggling with is that, well, we need some sort of criteria for how we capture any of this, so how can we register an opinion on it if we're not satisfied with the method by which any of this was captured? So I think that that -- so, therefore, if the label needs to reflect, and since we can't capture it, we're going to have to say everything, then that's what it has to say.

But, you know, there are theoretical ways you could explain all of those things in direct relation to nickel or anything, like other theoretical ways. They're not proven necessarily, but there are theoretical ways. And, again, with respect to the functional complaints like -- that can't be pinned down to a pathology, like a headache or a bellyache or something like that, you know, that can go along with a variety of general reactions to things, and this can be one of them.

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

I think for "other," we would kind of refer to what might be a new onset of autoimmune disease as we're kind of throwing in with the allergy and hypersensitivity, but it may be a totally separate phenomenon, is that is it related or not? We don't know. And we haven't really talked much about just hypersensitivity disorders in general where we -- you know, some people are hypersensitive; is there a relationship to IBS or fibromyalgia, and would these folks not be good candidates for an implant? And we don't know that either.

DR. IGLESIA: Dr. Fisher.

DR. FISHER: Dr. Janik, I just want to get clarification on your comment about pregnancy. There was talk about the need for long-term follow-up on outcome data, and then you had added something at the end, and I'm sorry, I didn't catch that.

DR. JANIK: That pregnancy oftentimes seems to happen because people don't come to their follow-up study, so there's a gap. But if before the procedure is placed you have your follow-up 3-month study paid for, organized, it's a package, you can't put it in until the second part's organized, so it's not, oh, well I guess we need to set it up, my insurance doesn't cover it, I can't afford it. You just can't start if you can't finish.

DR. FISHER: Got it. Okay, thank you.

DR. IGLESIA: All right. Dr. Coddington.

DR. CODDINGTON: Just one other thing. We've addressed some issues in dealing with the instructions to the person that is implanting the device.

DR. IGLESIA: Yes.

DR. CODDINGTON: The other that I think would be very helpful, and I did not see it, it may be there and if I missed it, I apologize, but is to give some instruction about how to interpret the HSG. In other words, there were some young ladies that brought the films up and showing that said my HSG is abnormal, something you could obviously tell, but --

DR. IGLESIA: This is Question No. 2.

DR. CODDINGTON: Yeah, okay. Sorry.

DR. IGLESIA: So if we're done with Question No. 1, I think we might be able to move to Question No. 2. Thank you.

MS. CHAUHAN: Cynthia Chauhan.

Could I ask one question of the FDA?

DR. IGLESIA: Of course.

MS. CHAUHAN: Following up on Dr. Chappell, I know that it is not usual to go back and say you have to do a randomized control trial, but it seems to me so many of our questions would not be here if that had been done directly in the beginning. Is that something you can never say?

(Applause.)

DR. YUSTEIN: I think one of the questions that we have coming up will ask you if you believe additional clinical information needs to be collected, and that'll give you the opportunity to provide us with further input on what you think it needs to look like and what needs to be collected.

MS. BLYSKUN: Elaine Blyskun.

Question 2: For each of the events of concern discussed in your response to Question #1, please discuss the clinical implications and possible risk mitigation strategies, such as changes to physician labeling, patient pre-operative evaluation or selection, or post-operative monitoring.

DR. IGLESIA: Who would -- we did talk a lot about this, but would someone like to just summarize and have a little bit more of a discussion?

Dr. Gardner.

DR. GARDNER: Yeah, Jim Gardner. So I did have a question related to that.

DR. IGLESIA: Sure.

DR. GARDNER: We discussed quite a few notions about changing practice protocols

and physician training. I think the Sponsor is probably wondering what would their involvement be in that, what should it be, who should be responsible for establishing these protocols and then doing the training. Is that sponsor, FDA, professional societies, medical school, training residencies? Any thoughts about that from the clinicians in the Panel?

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

You know, the question came up earlier when we were asking Bayer about, you know, someone does five procedures with someone watching them, and then who makes the call if they're trained or not trained, should get credentials? So industry manufacturers do not credential physicians; you have a local credentialing board that does. And some hospitals are going to, you know, absolute numbers in order to keep their privileges, so whereas if you don't do 10 of a certain procedure in a year, then you lose your privileges and you have to be proctored again.

Now, that applies to hospital settings, but there is no credentialing oversight in private practice offices and in a lot of clinics, so there's a lot of -- there's a lot -- I've given you a lot of questions to your question, because there is not one board who decides how many you have to do that makes you confident, if you have a problem, what happens. And when I looked at our data at our hospital a number of years ago, I looked at all the Essures done in a year and looked at -- we were looking at follow-up and complications. And we found that over 75% of the perforations were by one physician on a staff of like 45 people doing the procedure, and so that was one reason I asked the geographic to see if there are clusters of problems based on what can we localize into a certain place, a certain type of

hospital. There are so many things that we could learn from better tracking.

DR. JANIK: I agree with individual tracking, but I disagree with a specific *n* number because you can have somebody that does 50 and they're still perfing; somebody who does very few -- so that number correlation, I think, is -- gives a false sense of security. It needs to be tracking of outcome.

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: Yeah. But if you have a registry and you review it every 6 to 12 months, you're going to see something like that pop up, it will be a red flag.

DR. IGLESIA: Okay. I'm going to go around the table.

Okay, Dr. Baird.

DR. BAIRD: The tracking also would be much easier for problems if there was this after 7 days kind of an ultrasound or an immediate ultrasound because then you have something to go by, to track with, so it seems like we've discussed things that would make this much easier.

DR. IGLESIA: Great. So I mean, I just want to go around the table to see if anyone has anything additional to add about training, preoperative evaluation, or postoperative surveillance. I'll start this way.

Deb.

DR. MYERS: Deb Myers.

Yeah, thoughts that I've had to try and lessen perforation rates or unrecognized perforation would be like ultrasound, like either post-procedure or like within a week, just to kind of ensure where the placement is. A thought I just had off the top of my head now

is similar to the IUD, it has a string. You know, if you put a string on the end of it and if the string is gone, then you know the coil's gone somewhere. I'm just thinking in my head. Something to think about. I also think that maybe some more bolder, specific information needs to be given to patients. We've been talking a lot about autoimmune responses, what it is, whatever the condition is, but either a patient card, a patient guide, you know, kind of a highlighted bulleted piece as opposed to a big long list of lots of information.

DR. IGLESIA: Thank you.

Dr. Chappell, anything to add?

(No audible response.)

DR. IGLESIA: Dr. Coddington, anything to add to training, pre-op evaluation, or post-op?

DR. CODDINGTON: Sure. Charles Coddington.

I think the post-op aspect that I mentioned regarding the interpretation of the X-ray films would be helpful and then would make things more standardized as far as the post-op process, and I think the results would be all the more clear.

DR. IGLESIA: Can I just ask, is that like a quality control, like somebody's going to actually be a second set of eyes reviewing the films, sending it to --

DR. CODDINGTON: I think -- no, no. All I'm saying is relative to the uterine cavity, when you do an HSG, you can see where the device is.

DR. IGLESIA: Right.

DR. CODDINGTON: And it's -- the device lights up on X-ray, seen it, done it, been there, and it's just a question of is there something that if the device is not in the uterine

cavity, Houston, you have a problem? I mean, you know, in other words, if it's migrated out of the tube and that sort of thing. So that would be the point. And I think also in changing the physician training is to allow the physician to not pursue when the situation is not going to be easy, as you mentioned. If there looks like there's spasm, you can identify spasm when you're looking through the hysteroscope. This is not hard. And/or -- yeah, some of the comments, and forgive me, we've gotten them from everywhere, about looking at not getting good "visualization." If you don't have good visualization, you shouldn't be doing the procedure, or at least not at that time. So I think that giving some guidance allowing people to give up.

DR. IGLESIA: Dr. Janik, anything else to add?

(No audible response.)

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: There were two things that -- we talked about at 3-month procedure to verify that the instrumentation, where it's supposed to be, but we didn't talk anything about the additional contraception that people are supposed to be taking for those 3 months. So I don't know how much of that may or may not contribute to the pregnancy outcome, but it seems that that would be something that we could stress more than maybe what's already being done. The other thing is on the labeling. I think it says give a history of pelvic inflammatory disease, you shouldn't have this placed, but even though it seems so basic, I don't know if there's -- everyone's doing screening for STDs before they place this.

DR. IGLESIA: Ms. De Luca.

MS. DE LUCA: Jo-Ellen De Luca.

Thinking on the autoimmune diseases and being a person with a very limited immune system remaining, looking from M.D. to M.D., every doctor I go to gives me another drug or tries to, and so often, you know, I've gone from methotrexate to Remicade, Imuran, and I've taken the wide gamut; so have a lot of these patients for another reason. And I think maybe the response, if we could somehow make sure that all the physicians are on the same page and recognize what they're doing, because we might be overmedicating with autoimmune problems and then the device itself gets -- comes into question.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I do believe very strongly -- I understand that licensing is not the purview of the company, but I believe training is the ethical responsibility of the company, and part of that training should be what, I believe, was Dr. Coddington touched on, not only how to implant the device but when you refuse to implant the device. I think there needs to be far more rigorous screening of patients, taking into account some of the other risk factors that were briefly mentioned but we haven't gone into in great detail, like obesity, and really being willing to say this is not the best procedure for you and to help the patients look at other options as well as this option with a well-trained circuit of physicians.

DR. IGLESIA: Dr. Gardner, anything to add?

(No audible response.)

DR. IGLESIA: Dr. Wills-Karp.

DR. WILLS-KARP: I guess I'd have to say I'm amazed listening to the speakers today that their physicians allowed a lot of these abnormal events, bleeding, et cetera, to go on

for such a long time. And I just --

(Applause.)

DR. WILLS-KARP: -- think that it requires a lot more physician training. But the patients also should be told if these things persist past a certain period, you know, go and camp out at the doctor's office. Don't just let it go. Not saying they did, but it's also the physicians didn't seem to do the proper follow-up, and I think they absolutely have to.

DR. IGLESIA: Thank you.

Dr. Baird?

(No audible response.)

DR. IGLESIA: Peter. Dr. Schalock.

DR. SCHALOCK: Peter Schalock.

Just a thought. From dermatologic medications, Accutane or isotretinoin, every patient fills, reads, signs off on multiple points on a single consent form that's provided through a program at least monitored by the FDA. Maybe this would be something we could recommend, is develop a consent form, a uniform consent form for the patients that brings up our concerns. I mean, do you think you're nickel allergic? Okay, well, you know, you signed off on it. And that was some things brought up by the community speakers, that if they knew they were metal allergic or if they knew it was metal, they wouldn't use it. So I don't know what's happening, but something like that may be useful where, here are the things we need to know, and put it on a piece of paper that is a formal consent form.

DR. IGLESIA: Dr. Katz?

(No audible response.)

DR. IGLESIA: Dr. Stubblefield.

DR. STUBBLEFIELD: I listened to all those stories for 2 hours. There is a wealth of information there. Perhaps a lot of it is written down, at least on the websites, which I haven't looked at, but seems to me like we really don't have a full grasp of what this problem is. We can't really even agree for sure that there is a problem. It may just be that the device is a red herring, just to let you know you were going to get a fibroid and the fact that you've got this device didn't make you get the fibroid. But there's just a whole lot of details in here, and is there room for a sort of broad epidemiologic analysis, getting together a lot of the stories and writing them down and trying to see what's there and maybe what isn't there and think about other exposures, trying to get a better overall grasp of what the problem is?

DR. IGLESIA: Finally Dr. Milner.

DR. MILNER: So, just quickly, I mean, it was suggested before, but I do think it's important to point out that those who walk in already with -- you called them hypersensitivity. I'm not sure for all of them I would call them that, but if there is a substantial autoimmune history and a substantial history of functional complaint such as headache and IBS or other things of the such, until we have more information that that really isn't a risk factor, it's just -- and it's really the purview of the FDA to decide, you know, what trips that. But I'm sure that in plenty of our experiences, that putting someone like that through another experience, until there's data to prove otherwise, these types of things are going to come up, so at the very least they should be pre-identified, you know, in that regard.

DR. IGLESIA: Okay, thank you very much.

Any comments? I'm going to summarize otherwise.

Dr. Fisher.

DR. FISHER: I just had one follow-up question for Dr. Myers.

Dr. Myers, you suggested that it might be useful to have a patient card, and I was unclear as to if you meant that a card that you give the patient that really outlines what they're about to get into, or if it was a card that says I'm a card-carrying Essure patient, because it sounds like from a lot of these patients, they're getting passed around from doctor to doctor to doctor, and a lot of them don't even really know what this device is about. So I was wondering which one you were suggesting.

DR. MYERS: Deb Myers.

I was actually thinking of the first, more of a patient information, like this is the procedure, these are the kind of like key highlights of things you need to know, are you nickel allergic, do you have autoimmune, you know, history of infection. But, actually, I like your second thought as well. You're talking about "I have an Essure in me."

DR. FISHER: Right.

DR. MYERS: Right.

DR. FISHER: Right.

DR. MYERS: Yeah. I like that as well.

DR. IGLESIA: Okay. Dr. Seifer and Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

Following up on that, I like -- they've got a great resource over here at 1-800-CALL-A-

FRIEND, and I heard a number of people went to the ER and they went "huh," and to avoid that, have a card or something, "I've got an Essure; if you don't know what it is, call 1-800." They have that.

(Off microphone comments.)

DR. CODDINGTON: Oh, okay.

DR. FISHER: So it sounds like we have a good idea, but it's not being implemented very well across the board, so -- or it's not being -- or people aren't understanding it when they see it.

DR. SEIFER: So, in terms of patient labeling, it was brought up from the floor about whether or not this is really a nonsurgical procedure. I mean, given what we've seen in terms of the complications and the extent of them, maybe we should consider changing that.

(Applause.)

DR. IGLESIA: Okay. Okay, all right. Let me try and summarize here.

With regard to Question No. 2, in events of concern regarding training, there seems to be some additional training that is necessary, not just in the initial implantation with regard to going through the modules and the didactics, the simulation, and the preceptoring/proctoring of a minimum of five cases; we need to have some type of oversight afterwards so that we can see whether or not, and track whether or not, there are certain surgeons who are implanting who have higher than expected complication rates.

Number 2, the surgeons also need additional training in when to pull out, meaning when this is a contraindication, this is not going well, we should not be putting this in, you

know.

And, number 3, there needs to be additional training and/or resources available for the training for removal and particularly complicated removals for things that are fragmented, migrated, and/or -- you know, complicated with regards to the multi-modalities, the way you can remove this, either hysteroscopically, laparoscopically, and the kinds of dissection, short of hysterectomy.

With regard to preoperative evaluation, we had a lot of discussion about the consent form and whether or not there should be a checklist that includes screening for autoimmune diseases, other hypersensitivities, other -- headache, irritable bowel, history of pelvic inflammatory disease, or even current sexual transmitted screening and -- in order to develop a list of maybe even absolute or relative contraindications to undergoing this. And the patients need to understand that and maybe even have an official consent form which is gone over so we have understanding and signature.

Secondly, the preoperative evaluation, even including the intraoperative evaluation, may include additional imaging relatively soon, that where you placed it is where it's supposed to be, and/or if there are complications in the short postoperative period, that we get that imaging even before the 3-month mark. With regards to the postoperative evaluation, again, imaging comes out; we should have a checklist of complications that would lead to the additional imaging that may be needed. We should have a way to evaluate the quality of the interpretation of even that 3-month HSG or images that occurred that were indicated and taken even before that 3-month time period. Again, this speaks to the registry and to the development not just of the patient cards are given that Essure was

implanted but even perhaps a unique device identification number or some better way of tracking these. And guidance, more guidance is needed on the long-term management of complications.

Did we miss more --

DR. SEIFER: Is it too late to discuss whether or not it should be a surgical procedure or --

DR. IGLESIA: Oh, that's on the patient -- yeah. That's on No. 3. Patient labeling is the next question, so -- okay.

So, Drs. Fisher and Yustein, is this adequate? Or do you have any other questions for the Panel?

DR. FISHER: No, good. Thank you very much.

DR. IGLESIA: Oh, you're welcome.

Elaine.

MS. BLYSKUN: Elaine Blyskun.

For the events of concern discussed in your response to Question 1, please provide any additional general recommendations for modifications to the physician and/or patient labeling which might help to address that concern. If there are any additional other general labeling recommendations which do not pertain to a specific type of event, please provide those as well.

DR. IGLESIA: Who would like to begin this discussion?

Dr. Elser.

DR. ELSER: Denise Elser.

So I would like to respond to what Dr. Seifer said. I think there is certainly a precedent for plenty of intra-office procedures that we do that are not labeled as surgeries because there's no incision but certainly can have some serious adverse effects. So calling it a surgery, I don't think changes that you have to be aware of what serious events can occur and how closely to monitor for them and what to do if they occur.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

But a hysteroscopy is surgery. I mean, so just because --

(Applause.)

DR. JANIK: -- it doesn't have to have an incision doesn't make it nonsurgical, so to me all hysteroscopies are surgery. You could say placing an IUD is not surgery, but I think anything that's hysteroscopy is surgery.

DR. IGLESIA: Dr. Seifer.

DR. SEIFER: And the sorts of complications that come with hysteroscopy fluid overload and all the ramifications of that. And to Bayer's credit, they say, you know, if you have a 1500 cc deficit or it's taking more than 30 minutes, you should stop. I mean, those are the same kind of warnings that we give for doing hysteroscopy in the OR.

DR. IGLESIA: Are there -- oh. Anything on this side with regard to patient labeling?

Dr. Baird.

DR. BAIRD: Dr. Baird.

It seems to me that the current labeling, which I read the whole material, is very benign, and there's no indication of the possible need for removal and what the

ramifications of that can be. And so I think at least more information needs to be given about possible adverse events.

(Applause.)

DR. IGLESIA: Dr. Milner, do you want to piggyback?

DR. MILNER: Yeah, I just -- so I guess we mentioned it, but here is where the appropriate time is, which is that you can't limit the hypersensitivity warning to nickel allergy.

DR. IGLESIA: Ms. Chauhan.

MS. CHAUHAN: Is it appropriate for part of the patient labeling to be to tell the patient be sure that you have discussed in detail the risk of this procedure with the physician before proceeding? And the --

DR. IGLESIA: Sure. That's part of the informed consent.

MS. CHAUHAN: The risk factors.

DR. IGLESIA: Yeah. Yeah, so part of the informed consent would be talking about not only the benefits of a procedure but also the risks and the potential alternatives as well.

MS. CHAUHAN: I agree. That's -- and I've got that down in my notes, informed consent is very important. But this is even pre. This is when you're looking at the label. In case someone got sloppy and went through the informed consent too quick or said here, this is really good, you know. That's just another stop to say this is a serious procedure, to be thought about seriously, and to put something like that in the patient labeling.

DR. IGLESIA: And so I just want to just put -- so are you talking about, like, mentioning the development of new pain, abnormal bleeding, plus the potential for

migration/perforation?

MS. CHAUHAN: I wasn't even being that specific. I certainly don't object to that.

DR. IGLESIA: Okay.

MS. CHAUHAN: What I was saying is something in the patient labeling saying be sure you have discussed with your physician the risk --

DR. IGLESIA: Okay.

MS. CHAUHAN: -- and issues in this procedure before proceeding.

DR. IGLESIA: Got it.

Dr. Katz.

DR. KATZ: Just to elaborate -- David Katz.

I think the take home message here is that we want to provide information for the woman that she can acquire going into that visit where she has that interaction with the physician about the possibilities so that she already has relevant and necessary information to be self-informed as she goes into that first experience, that consult.

MS. CHAUHAN: Cynthia Chauhan.

Exactly. So that she goes in with a knowledgebase.

DR. KATZ: Right.

DR. IGLESIA: Ms. De Luca, do you have any other recommendations for patient labeling?

(No audible response.)

DR. IGLESIA: Okay, all right. I think I'll summarize.

Oh. I'm sorry, Dr. Stubblefield. I didn't see you back there.

DR. STUBBLEFIELD: We've had a lot of talk about, too, lumping things all together to begin with. Autoimmune disorders, some people appear to have developed them while wearing the device. Are we concerned about people that already have these autoimmune disorders? Should they know that this perhaps might predispose them to something else?

(Applause.)

DR. STUBBLEFIELD: That said, the downside of that is people that are already sick are going to be much safer having a hysteroscopy under a local than -- or general anesthesia for an alternative tubal ligation.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

The main thing that concerns me about that, it may be true, but we really don't know. So I hate to write something down that's saying, you know, if you have autoimmune, you shouldn't have this; we really can't say it. So I think you can say possibly, because we have some possible indications, but I don't think we should overstate without data.

DR. IGLESIA: Okay. Any more comments?

(No response.)

DR. IGLESIA: I'm going to try and summarize with regard to patient labeling and even general labeling, that this is a surgical procedure that requires the insertion of an instrument called a hysteroscope to place a device, and that's a permanent implant. I think that people need to understand that, you know, that -- what that implant is made of and that that implant may need to possibly be removed at some time, and sometimes the removal can be complicated. In addition, there may be some possible concerns for people

who have known hypersensitivities to X or underlying autoimmune diseases and that more data is needed for that. And I think that's it. I think the most important thing, though, is what Ms. Chauhan said, is that there has to be some kind of checklist to say that this discussion actually happened and so that, you know, the patients are aware and some documentation made.

Dr. Yustein, Dr. Fisher.

DR. YUSTEIN: So if I can just address a comment that Ms. Chauhan made and that you just talked about, Dr. Iglesia. We do have a couple of examples where we have patient information brochures for some PMA products where the last page is kind of a checklist that recommends that the patient and the physician both initial by each item and it goes down several different things and says we discussed this and the patient initials it, the doctor initials it. We do have a couple of examples where we have asked companies to do that at the back on the last page of the brochure. Now, again, FDA doesn't intervene in patient informed consent procedures and whether or not that takes place at the office level between the patient and the physician. You know, the document would help promote that, but it wouldn't guarantee that that discussion takes place.

MS. CHAUHAN: So that's not within -- Cynthia Chauhan.

That's not within the purview of the FDA's authority?

DR. YUSTEIN: We can ask the company to put something like that on the patient brochure, but we certainly can't be in the room watching the patient and the physician initial each item and make sure that that takes place.

MS. CHAUHAN: Cynthia Chauhan.

So you cannot mandate an informed consent, beyond the brochure? You cannot mandate an informed consent --

DR. YUSTEIN: Right. The brochure is more of an informed decision making; it's giving information. But the informed consent process is really the patient-physician process.

DR. IGLESIA: Dr. Fisher, then Dr. Seifer.

DR. FISHER: Yeah. We're splitting hairs here, and it is kind of an informed decision form because informed consent is really, it's really tied to an investigational device. I mean, that was the intent, that's our authority for informed consent, actually deals with an investigational device. So this is something that we're talking about, it would be an informed decision form or something, but it wouldn't be called an informed consent.

DR. YUSTEIN: So I think what -- sorry. Dr. Yustein.

I think what Dr. Fisher is clarifying is that in the case of an IDE study, certainly FDA reviews the informed consent document and has input with the company on what should be in those informed consent documents, but for a procedure like this for an approved device, we don't regulate the informed consent document that a physician and a patient would have in their office.

MS. CHAUHAN: Cynthia Chauhan.

So if it gets moved to being a surgical procedure, then can you demand it?

DR. SEIFER: You don't have to.

MS. CHAUHAN: You don't?

DR. SEIFER: Sorry. David Seifer.

You won't have to because it's a surgical procedure, and that requires informed consent.

MS. CHAUHAN: That's what I was saying.

DR. SEIFER: Yeah.

MS. CHAUHAN: Yeah.

DR. IGLESIA: Okay. Dr. Fisher, Dr. Yustein, is this adequate or do we have other -- for Question No. 3?

DR. FISHER: I think we're good. Thank you.

DR. IGLESIA: Okay.

Elaine.

MS. BLYSKUN: Elaine Blyskun.

For the events of concern discussed in your response to Question #1, please discuss whether you believe any additional post-market bench and/or clinical data should be collected by the sponsor to better understand the events or inform mitigation strategies.

If so, for each outcome, please comment on the following:

a. The patient population to be evaluated

b. The clinically relevant endpoint(s) to be assessed

c. Appropriate duration of follow-up

d. Ancillary tests (e.g., labs, imaging, etc.) that should be conducted

DR. IGLESIA: Okay.

DR. SEIFER: So if you have a registry, I wonder who should be in charge of that. It may not be the best option to have the sponsor running that, but I don't know who the best

monitor of that would be.

DR. IGLESIA: You know, I have been involved in the development of several registries, and I'll just disclose that vaginal mesh was one of them. And the industry as well as the FDA, as well as the relevant medical societies and patient representatives, as well as insurers were all involved in the development of that for the postmarket surveillance and to answer some of the 522 orders that were then eventually initiated, so it is possible to be done. So that point is well taken, a registry of the relevant parties, including patient representatives. For the patient-centered outcomes.

Other discussion? Grace?

MS. CHAUHAN: Cynthia Chauhan.

Is this where we talk about another clinical trial?

DR. JANIK: That's exactly what I was going to say.

MS. CHAUHAN: I am mindful that there are a large number of women who use this device successfully, and we're not addressing those today, but I'm mindful that they exist, that sterilization is an important option for women. I would really like to see a randomized control trial done with a population, a control population, and that would, I think, address some of the issues that Dr. Milner brought up about some of these symptoms happen to people because of trauma, whatever the trauma is, and if you've got a control set, you could begin to clarify some of that. I think given the large population that's affected, the differences in outcomes, another randomized -- not another, there wasn't one. A randomized control trial would be an appropriate thing to look at for this device.

DR. IGLESIA: Dr. Janik, then Dr. Elser.

DR. JANIK: That's really what I was going to start to say, and I think that it's more important; I think we have pretty good pregnancy outcome data. I don't necessarily think that's what our endpoint is. I think our endpoint is more what kind of complications and symptoms do we have coming off of one form of birth control going to tubal ligation, standard tubal ligation versus Essure. Is it the same, this bleeding profile? How many people go on to develop autoimmune issues, reactive issues? We assume it's the device, but unless we compare, we'll never answer the question.

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

My concern would be that we don't really know that denominator or the incidence of how many people may or may not have autoimmune problems. Could we power a study to be able to capture rare events, you know, given the expense of an RCT? And how many patients, how long do you follow up, how do we figure out how to power it?

DR. IGLESIA: Other comments?

Dr. Stubblefield.

DR. STUBBLEFIELD: Just a little wild guessing. I mean, if the phenomenon we're talking about, if this is 1 or 2 per 1,000 patients and the sample size gets us something that the Defense Department would have to support, no one else could afford it.

DR. IGLESIA: Okay.

DR. WILLS-KARP: Some power issues. I think some of this information may come out of --

DR. IGLESIA: Just state your name, sorry.

DR. WILLS-KARP: I'm sorry. Marsha Wills-Karp.

I think some of the information that's needed or in the complications may come out of the registry.

DR. IGLESIA: Yeah.

DR. WILLS-KARP: Prospectively.

DR. IGLESIA: Not necessarily RCT.

Dr. Katz.

DR. KATZ: David Katz.

Another question would be is there any more that we can learn from the ongoing studies? Now, the big study is in Europe, it's not here, that the Sponsor is conducting. And we asked all the questions that need to be asked from the data that exists to date and from anything that's ongoing now. It's already underway.

DR. IGLESIA: Okay.

Final comments? Let me --

Oh, Dr. Gardner.

DR. GARDNER: This is on a somewhat different topic. We've been talking about needing histopathologic evidence.

DR. IGLESIA: Yeah.

DR. GARDNER: And I'm wondering, is it standard of care today if there's an explant done, is that specimen sent off to path for assessment? And if so -- I see some heads going up and down and some -- if so, are we sitting on that data now, and can we work with the patient groups and identify people and get their consent to share their records and get that

information?

DR. IGLESIA: Okay. All right, let me try and summarize Question -- the answer to Question No. 4, then.

DR. FISHER: Before you do --

DR. IGLESIA: Oh.

DR. FISHER: Sorry. Dr. Fisher.

DR. IGLESIA: That's okay, Dr. Fisher. Go ahead.

DR. FISHER: Yeah, Ben Fisher.

We have (a), (b), (c), and (d) up there, and I really didn't hear anything specific. I heard randomized control clinical trial --

DR. IGLESIA: Got it.

DR. FISHER: -- but I didn't hear anything about patient population, I didn't hear anything about endpoints, duration, and we would really like to have your input on if you're to say that you want another randomized control trial. What exactly would you be looking for?

DR. IGLESIA: We talked a little bit about the endpoints with regard to complications versus pregnancy rate, and we really didn't talk a lot about the duration or ancillary tests.

DR. FISHER: Or the population.

DR. IGLESIA: Or population.

DR. CHAPPELL: At the risk of repetition and giving words that burn in my mouth as they leave it, this is too late for a randomized controlled clinical trial, and that I agree with Dr. Katz' and others' suggestions that we piggyback and get the best information we can in

2015. But to those at the FDA, perhaps I shouldn't mention Congress, I would suggest that a randomized clinical trial is the way to go for the future. Other devices.

(Off microphone comment.)

DR. IGLESIA: Oh, put your mike on.

MS. CHAUHAN: I'm sorry. Cynthia Chauhan.

Could you clarify why you think it's too late? Because we're talking about a device that will be used for a long, long time if it stays approved.

DR. CHAPPELL: Rick Chappell.

Perhaps I shouldn't be so negative, but I really worry about accrual. I do have some practical intuition, and if I were to try to convince a clinician or her patients to enroll in a clinical trial because we have grave concerns about the safety of a device, that would not be a big selling point. It's hard enough to randomize device trials, surgical trials at any rate. It's easier to randomize two pills, but there's enough challenges. I just don't think it would accrue.

DR. IGLESIA: Dr. Seifer, Dr. Coddington.

DR. SEIFER: I mean, maybe we approach this in stages. We do the registry, we see what the real incidence is, we get real numerators, denominators, then we think about doing an RCT that's going to cost and take so much time to do. We'll see if it's really determined if these are real recurring issues.

DR. IGLESIA: Do you have an opinion about the patient population or the length of follow-up?

DR. SEIFER: With regard to the registry? I think it should be, for now, pretty much

indefinite. I mean, until -- or at least for the foreseeable future, and it should be reviewed every 6 to 12 months so you can see what's coming up.

DR. IGLESIA: Yeah. I know that the vaginal mesh registry was a 3-year endpoint. I mean, there's some feasibility issues here. And it was not a randomized trial. The 522 studies are actually prospective cohorts with a shared -- tissue arm and the vaginal mesh arm. It's every 6-month follow-up for 3 years with real patient-centered outcomes that patients can populate regardless of which position they're seeing.

DR. SEIFER: Some of the comments we've heard here, they have developed over some long period of time, so I --

DR. IGLESIA: Yeah.

DR. SEIFER: You know, depending upon the reality of the situation, I would think 3 years a minimum. I'm thinking more like 5.

DR. IGLESIA: Five years.

DR. SEIFER: Yeah.

DR. IGLESIA: Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

Thank you for bringing up the mesh because, I mean, that's a perfect model to -- perfect model. Not paralleling, but in other words, every 6 months for 3 years we've got some 5-year data here that may guide us a little bit about whether there were things that came up. I haven't looked at that data specifically to see if you had some increased incidence of problems and that type of thing. But I think looking at it in that regard will help us. So I think, you know, patients that have the Essure, patients -- I think if we want to go 1

to 5 years with the aspect, we could be more specific if we see something at 1 year, if there are things that really jump out at us in regards to either application or complications of the way in which the device is implanted, that's going to come out quicker than something dealing with autoimmune.

DR. IGLESIA: Yeah.

DR. CODDINGTON: So I think that this is something that can be done in a very positive and ongoing way to help evaluate, as well as patient care.

DR. IGLESIA: Thank you.

Dr. Wills-Karp. And do you have -- any other ancillary tests? Okay.

DR. WILLS-KARP: First, I was going to say I don't think it makes sense to do a randomized trial at this point because you're not going to have the power to pick up some of these events with the size studies that are generally done, so I don't think that would change the data that's obtained. I think it's more relevant to follow the registry of these folks and see what's happening actually. And it's the length of time that sort of revealed the number of these issues, complications. Other tests, I think we've sort of said it several times, but trying to figure out exactly what some of these immune changes are, adding those on. Certainly, nickel and whatever the types of tests, we probably need to have more extensive conversation about that. But just put that in the record that they need to find out more carefully what are these actual immune responses.

DR. IGLESIA: Dr. Milner.

DR. MILNER: Just briefly, just to follow up. It was brought up, I think, by someone else, but to put it into here, which was that, you know, the standard for nickel leaching, and

honestly, we probably should look for everything else, is to put it in water or saline, I forget what it is, but it would seem to me that the better assay here would be to put it into -- whether it's, I don't know, an animal or something like that and to actually try to measure within the tissue if the amount that's being released is more than you would have thought it would have been instead of just putting it in water, which doesn't -- not really what's happening here.

DR. IGLESIA: Okay. Dr. Janik.

DR. JANIK: I do think that patients that are having these removed are a very useful source of information, and maybe we should do something expanded with that subgroup.

(Off microphone comment.)

DR. JANIK: I thought it's No. 4.

DR. IGLESIA: No, it's part of it. Patient population.

DR. JANIK: Okay. No, no. As far as a population --

DR. IGLESIA: Yeah.

DR. JANIK: -- to follow the path, maybe we want more than standard path. I don't know what testing you guys would recommend with the tubes that are removed. Also, some expanded history of what brought them to that situation, then their outcome of removal.

DR. IGLESIA: Okay.

DR. JANIK: I would add that onto that subgroup.

DR. IGLESIA: Okay, I'm going to try and summarize now, then.

So the question regards postmarket, bench, and/or clinical data that should be

collected by the Sponsor to better understand events in order to inform mitigation strategies. Population of patients to be evaluated include patients who have had complications and have had removal, that necessitate removal, and we would want to know what -- their symptomatology, the history, and what -- obviously, an evaluation of the actual pathology of the removed device and/or tissue surrounding it. Another population of patients are those who are currently enrolled in clinical trials and trying to extend that past, beyond, the 3- to 5-year duration, specifically looking for outcomes that are a little bit more rare like some of the autoimmune disorders in addition to the ones we've already mentioned with the complications.

It seems that, in terms of a clinically relevant endpoint, we're all aware that if properly done in a proper -- the method has been completed and the follow-up imaging shows occlusion, that the pregnancy rate is okay, may be comparable, but the complications are something that we're a little bit more interested in, in terms of a clinically relevant outcome. Is that correct? Overall and general. But it is a process that needs to be looked at, so complications even over pregnancy prevention.

And then, finally, in terms of study design, we have some concerns about whether or not a randomized clinical trial is practical or even feasible at this point, given the social media and the negative outcome on this. However, we do feel that postmarket surveillance of these devices is necessary and that a registry would be useful in that way, and the registry should include pretty significant close follow-up, whether it be every 6 months, every 1 year, and if we can extend it past 3 years to even 5 years or longer, if feasible, particularly for some of the more rare outcomes. I think -- you know, we talked about

seeing some of that with regard to the ongoing studies, but the problem is, is that we would like to compare that, have some kind of comparison group, which you can do in a registry with prospective cohorts, which we can't do currently with the PMA trials and the premarket studies that we have in place.

Dr. Baird.

DR. BAIRD: I'd like to consider also adding some sort of imaging to the ongoing study for a later time --

DR. IGLESIA: Oh, right.

DR. BAIRD: -- other than just the standard imaging.

DR. IGLESIA: Yes, I didn't mention the ancillary tests and the other imaging. You know, we need some other, not just post-procedural, the 3-month, but possibly even some delayed imaging to understand better the migration/perforation issues and also the blood tests, skin test, bench, xenografts or whatever we're using in terms of animal models for how the tissues act, the device is acting in vivo in animate and human subjects.

Dr. Yustein, Dr. Fisher, does that summarize, or do you have more questions?

DR. YUSTEIN: So can I make one comment and then a couple questions? So I believe that the TVU study is a 10-year study?

DR. FISHER: Yes.

DR. YUSTEIN: So that study still has many years to accumulate data, just to point that out.

DR. IGLESIA: That's good.

DR. YUSTEIN: So, in terms of outcomes that would be evaluated in a prospective

trial, whether -- whatever form that looks like, can we get a little bit more definition from the Panel in terms of are they the items that we've generally been speaking about for the last couple of hours? Are there other patient-centered outcomes or adverse events that we haven't mentioned that should be particularly tracked in a registry or whatever form that we do this?

And then my other question is there seemed to be a lot of talk earlier today about various bench testing related to allergies and nickel testing and things like that. Are there any other nonclinical evaluations that the Panel believes is necessary to further evaluate?

DR. IGLESIA: Dr. Chappell.

DR. CHAPPELL: Rick Chappell.

Removal.

DR. YUSTEIN: Right. That's the ultimate rejection of the intervention, is to have it reversed.

DR. CHAPPELL: Right.

DR. YUSTEIN: And I heard that that was one outcome that, in particular, we want to be following, and the outcome of the patient symptoms following removal, so certainly we heard that. Are there other particular ones other than the items we've kind of focused on throughout the day? Are there other outcomes or adverse event types that should be specifically captured?

MS. CHAUHAN: Cynthia Chauhan.

DR. IGLESIA: Yes.

MS. CHAUHAN: When you say the ones we focused on today, are you talking about

the small group or the long list?

DR. YUSTEIN: Well, I was referring to the ones that we've been speaking about during the question and answer session. We've been focusing on things like vaginal bleeding irregularities, metal hypersensitivity. I don't want to, you know, mischaracterize that, that quote. Perforation, migration, removal. Those are the things we've been focused on, but certainly you saw the longer list, you've heard other issues from patients in the audience, so I just want to make sure that we have that discussion.

MS. CHAUHAN: Cynthia Chauhan.

I think -- I don't mind giving you work. I think it should be the long list because that's going to filter out, to help filter out where focus needs to be. If we just do the top five, then you may be losing some really important information.

(Applause.)

DR. IGLESIA: I think what you're referring to or alluding to is some more of the quality-of-life issues. I mean, there was some concern about dyspareunia, the overall fatigue, the depression, the headache. And, you know, certainly we have validated questionnaires like the SF-36, and we have validated questionnaires like the Female Sexual Function Index, you know, that can be added, because you don't know what you don't know.

DR. YUSTEIN: On the other hand, you know, I'm not a registry expert, but if you have a list of 400 things that you're asking a physician to check off, how accurate is that going to be? So somewhere along the way we need to focus it down to --

DR. IGLESIA: Yeah.

DR. YUSTEIN: -- a feasible set of items, and I just wanted to try to get an idea from the Panel which they thought were the most feasible, because although I agree the list of several dozen things would be nice, I don't think that's going to be realistic.

MS. CHAUHAN: Cynthia Chauhan.

That's why PROs are important because you don't just filter through the physician; you get direct information from the patient that's validated.

DR. IGLESIA: Yeah. Patient reported outcomes.

Dr. Fisher, do you have any other questions or comments that we --

DR. YUSTEIN: I'm sorry, can I?

DR. IGLESIA: Oh. I'm sorry, Dr. Yustein.

DR. YUSTEIN: Can we go back to the -- was there anything from the preclinical standpoint? I just want to make sure we covered that.

DR. IGLESIA: Oh.

DR. YUSTEIN: Was there any --

DR. IGLESIA: Dr. Milner.

DR. MILNER: It's hard to know what the question is to ask. I mean, make up a great model in vivo, intra-organ model for nickel hypersensitivity, that would be great. I don't know when that's going to happen, you know; that's not an easy thing to accomplish.

DR. YUSTEIN: So you're not aware of anything that's obvious and easy right off?

DR. MILNER: There are plenty of models of surface sensitivities which lead to some of the stuff that's being discussed here, but this is a different story. And certainly, you know, implanting this into mice or something else for a longer period of time and really

following it and seeing what happens, but I don't even know that you're going to get the outcome you're looking for when you do that. So without a model, you know, I -- it's certainly worth -- I should make it clear that, you know, we're not complete experts on nickel allergy, and so diligence should be done that if such a model does exist, that that should be found.

DR. YUSTEIN: And, sorry, can I ask Dr. Milner one more question?

Sorry, Dr. Milner. I'm going to ask you the same thing you asked us earlier. How would you define, if you're asking clinicians to check off a box that said hypersensitivity or allergic reaction, how would you define that?

DR. MILNER: So I think what I was more asking was, was there a standard that was being held? What my definition is and what everybody else's definition is, it's going to be different for different people, but the fact that an a priori standard didn't exist was what was disturbing me. And so I think that it's well known what an immediate hypersensitivity looks like, it's well known what a delayed type hypersensitivity looks like; when it's inside of your body, that's not well known. And so at least to be able to capture the things that are known, you'll be able to report them. What bothered me is that we said that the hypersensitivity rate was zero, and there were four things in there which I would have called a hypersensitivity.

DR. YUSTEIN: Thank you.

DR. IGLESIA: Dr. Fisher, are you satisfied?

DR. FISHER: Yes, thank you.

DR. IGLESIA: Okay.

Elaine, Question No. 5.

MS. BLYSKUN: Elaine Blyskun.

The current physician labeling provides information related to "Insert Removal," focusing on the technique of removal of an intra-fallopian insert via salpingotomy or salpingectomy or of an intraperitoneal insert with the use of fluoroscopy.

Please discuss and provide any further recommendations regarding the decision to pursue hysteroscopic or laparoscopic removal of Essure inserts.

In particular, please consider the following scenarios:

a. Patient having persistent abdominal/pelvic pain without objective evidence of insert malpositioning, migration, or perforation
b. Patient having persistent abdominal/pelvic pain with evidence of malposition, migration or perforation
c. Asymptomatic patient found, or suspected, to have device malpositioning, migration, or perforation on standard follow-up imaging (e.g., 3 months or following unintended pregnancy)
d. Other scenarios you deem relevant

In addition, please provide any comments regarding the current instructions for removing inserts.

DR. IGLESIA: Okay, Dr. Elser. And if you want to take a particular scenario, let us know.

DR. ELSER: Okay. Just a few comments. Denise Elser.

I want to make sure that we don't say that if a patient develops pelvic pain, that we

assume immediately that it's caused by the implant. So even if it looks like it's not in the perfect position on ultrasound, do we want to make this patient undergo a major abdominal surgery if other causes of pain haven't been addressed? So keep in mind that we, as pelvic specialists, see all the time kidney stones, constipation, myofascial disorders that occur in women with or without implants. So we don't want to say pelvic pain, get an ultrasound; doesn't look like perfect position, operate. And then, secondly, I would say that consensus among hysteroscopists, I've often heard is that if there's more than the eight trailing coils, more than expected, and you're relatively recent to the implant, you would attempt a hysteroscopic removal, and otherwise you would attempt it laparoscopically or by laparotomy.

DR. IGLESIA: Other comments?

Dr. Janik.

DR. JANIK: I think if the problem is relatively immediate, it's different than chronic, and chronic is when endometriosis, all the other things you mentioned, get to be more of the issue. It's immediate, it doesn't seem in the patient's best interest to make it go on when, you know, it happened right after the event, it's not clearing, and especially you get more problems with all other types of infectious issues and gets more -- or inflammatory issues. It's more difficult to operate, too, when you get past that window. So I think we have to think of it as two different problems. And I also think it's difficult to have one way of removing it. This is where I think you just need to have a very high skill level surgeon because it depends on what it's poking into and what's tangled up with it. So you can't have a formula of how to remove it.

DR. IGLESIA: Should we just tackle the question and let's do patient, let's do (a) and let's talk about it, immediate. So you have a patient with abdominal pain, it looks like it's in -- the device is in good position. She has pain and it's immediately after, not chronic.

(Off microphone comment.)

DR. IGLESIA: Under 3 months because chronic pelvic pain is generally defined as greater than 3 months, right?

Dr. Coddington.

DR. CODDINGTON: Charles Coddington.

I was thinking that we have the data that Grace alluded to earlier, of a week. So I mean, you know, if there's -- obviously, if there is extreme pain and there's concern by the physician of perforation, one has to have clinical suspicion and do probably an ultrasound right then and there.

DR. IGLESIA: Okay.

DR. CODDINGTON: If there is a comfort level of 3 to 5 over 10, then maybe okay, wait a week and then see where you are. I think there has to be some clinical aspect to that. I know that's not very specific, I apologize, but I think that the week is where we have some data to work on.

DR. IGLESIA: Okay. So immediate pain, we'd need some kind of imaging.

DR. CODDINGTON: Um-hum.

DR. IGLESIA: We would probably want to try some type of medical management of pain, assuming that there's no acute hemodynamically --

DR. CODDINGTON: Agree.

DR. IGLESIA: -- unstable situation going on like sepsis or something.

DR. CODDINGTON: Yeah.

DR. IGLESIA: And then -- but if it persists despite medical management and it's in the right position and it's in the wrong position, those are -- how would you like to proceed?

DR. JANIK: Grace Janik.

I think if it's the wrong position, on you go. That's the easy one.

DR. IGLESIA: Yeah.

DR. JANIK: And I think if it's in what -- I think our confidence of cracked position maybe isn't as great as we think, so I think if you're out past -- I'd give it at least a week because 99% were okay within a week. But if you're out a week, then I think it's -- I think you need to require 3 months or --

DR. IGLESIA: Yeah.

DR. JANIK: -- leave people go on and on.

DR. IGLESIA: Or maybe we should just get a second opinion with regard to the review of the imaging, you know. It seems like some people had some issues with the interpretation of the imaging. So that might be another thing to recommend.

Other comments on this side?

Dr. Myers.

DR. MYERS: Deb Myers.

Not really having expertise in this particular thing, but if you have just done a procedure, you are now a month -- it looks like it's in the right place but the patient's having severe pain, I would think you'd just go take it out. I mean, assuming ultrasound and

everything else --

DR. IGLESIA: And potentially go to Plan B with another form of like a laparoscopic tubal ligation. And I think that that conversation, you know, we probably need to have that kind of conversation so that that's not a failure of the surgery; it's just this wasn't the right procedure for this patient.

DR. SEIFER: You could potentially have that discussion in your informed consent, right?

DR. IGLESIA: Yeah, yeah. So I think that the asymptomatic patient with it in the wrong place is going to be a little tricky. Does anyone want to bring up this discussion?

Good. Dr. Stubblefield.

DR. STUBBLEFIELD: Doesn't this describe some of the pregnancies?

DR. IGLESIA: Yeah.

DR. STUBBLEFIELD: Isn't this the group that's going to be rich in unwanted pregnancies? So maybe you should go ahead and evaluate these people laparoscopy, if needed, now.

DR. IGLESIA: They're not having any problems, but the 3-month follow-up was not conclusive that this was close.

DR. STUBBLEFIELD: Right.

DR. IGLESIA: Or you know that this is in the wrong spot. You think it's better to preemptively go ahead and remove and do something correct, like --

DR. STUBBLEFIELD: Yes,

DR. IGLESIA: -- for pregnancy prevention?

DR. STUBBLEFIELD: Yes.

DR. IGLESIA: Okay.

Dr. Milner.

DR. MILNER: Yeah, it's on the point, although it really, in the end, is a question. And that is, are we already missing some of that data in the intent-to-treat, those who were missed in the intent-to-treat data? I mean, it's not an insignificant number of folks who were missed, and is it possible that that would be -- by missed, I mean they didn't complete the study, not that they weren't followed up. Is it possible that that data exists and they just have not been fully, properly made public? That is to say, meaning that there has been an examination of those who dropped out, either because of pregnancy, and was looked at. You know, the ultrasound was looked at, or at some point in time it was looked at in some way or another. Might we have a bit of a clue already that it exists right now?

DR. IGLESIA: So you're looking at it from a research question, what can we do on a secondary analysis of these failures with regard to the device location and the cause for the failure.

Dr. Janik.

DR. JANIK: Grace Janik.

I have other concerns because it's something that's reactive, so even if they're not asymptomatic at the moment, you're reactive in the peritoneal cavity, how do you know that it's inert and nothing is going to happen down the road? I feel like you have an obligation to take it out by the nature of what it is. Also, do we have any sense of how many people are like this? Asymptomatic but not positioned?

(Off microphone response.)

DR. IGLESIA: Yeah, we can't -- we're not addressing that. It's -- the question right now. But that's, you know, that's a scenario that is likely to exist because again, you know, we don't know.

Okay. Dr. Katz.

DR. KATZ: That goes into this question of what data do we need to acquire.

DR. IGLESIA: Right.

DR. KATZ: And, in fact, what we could learn, that's number -- is in 4. It's one of the questions that --

DR. IGLESIA: Right.

DR. KATZ: -- we would need to ask.

DR. IGLESIA: Yeah. And that's another where some prospective cohort registry would be able to answer those kinds of questions as well, because you'd have another outcome, being the imaging that is done post-op.

Okay, so that was all acute. How about the chronic? I guess, like -- how about chronic pain past the 3-month mark and a perfectly positioned device?

You would take it out.

DR. JANIK: I think you have to have your mind very open to other possibilities.

DR. IGLESIA: There you go.

DR. JANIK: You can't just assume it's the device. So you have to work them out, as any other chronic pain patient, and rule things out and -- but it's on your list. But it can't be so exclusive.

DR. IGLESIA: But it does bring up the question as to, you know, whether or not chronic pelvic pain may even be considered a relative contraindication, you know, to getting this device in the beginning. I mean, it is something that we're very aware with when we're doing implant as a pelvic reconstructive surgeon, so just something else to consider.

DR. SEIFER: I think that's a great point. I mean, that should be a contraindication in putting the device in.

DR. IGLESIA: Relative, relative. Okay.

DR. JANIK: Grace Janik.

Because it may be somebody's had multiple laparotomies, so I think you have to think it out, but it just adds confusion, so you want to --

DR. IGLESIA: Okay.

DR. JANIK: -- definitely weigh it.

DR. IGLESIA: Okay. Any more discussion? And I'll try and summarize.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I think that points to the importance of a really good pre-procedure history-taking where you bring up things that people may have begun to have some issues, but they don't know how to name them yet, and so you bring that up. And just a really good history beforehand.

DR. IGLESIA: How about the other scenarios that we may deem relevant and the way to remove these things? I think we probably need to discuss that.

DR. JANIK: I think the allergic and autoimmune will be a reason to remove also.

How do you determine when the hypersensitivity person should be removed? General unwellness, want to remove. I think that's a difficult question, but if --

DR. IGLESIA: I know. All right.

DR. JANIK: I think it's on the list.

DR. IGLESIA: Let's summarize. So with regard to removal, and we know the general comment with the approach, maybe there isn't the number of coils that are actually showing and the way that the imaging is, if this is very distally migrated, it may dictate the approach. It would be probably the rarer thing that you can probably just easily redo it hysteroscopically if some of these are very distally migrated or you have very few coils that are able to be seen outside the tubal ostia.

So for those who have abdominal pain that is in duration related to the insertion and it's something that was temporarily related to the insertion of this and it's failed the medical management, we would probably recommend removal. For those who have pain in a perfectly positioned device, then -- and it's past -- you know, we've done all the testing and it's past the 3-month mark, we may want to just think about the differential diagnosis for chronic pelvic pain and think about that. But it begs the question as to whether or not chronic pelvic pain, in and of itself, would be a relative contraindication for device insertion to begin with.

For those who have pain with evidence of device malposition, removal is recommended, whether that be acute or chronic. And then for those who are asymptomatic with a device that is not in the right spot, i.e., found because they became pregnant, device removal and another form of birth control is recommended. In terms of

the other scenarios, if you develop a de novo autoimmune hypersensitivity, some type of reaction, we feel that some consideration to device removal sooner than later should be given.

(Off microphone comment.)

DR. IGLESIA: Tweak it, yeah.

DR. MILNER: I would just throw in there that there is a significant risk in making that worse, as well, by going through that procedure, as well. So until we have a better sense of who the people are who are developing it versus in whom this is, you know, sort of a ball that's rolling, that recommendation could end up being harmful.

DR. IGLESIA: And so would you be so bold as to say that that would be a relative contraindication to putting this, if you know you have --

DR. MILNER: Beforehand, fine.

DR. IGLESIA: Yeah, okay.

DR. MILNER: But if someone has developed it de novo, I'm just saying I would be careful about how strong of a statement one makes --

DR. IGLESIA: Okay.

DR. MILNER: -- about whether to advise to remove at that point of time.

DR. IGLESIA: Point well taken. More data needed on the de novo development of autoimmune or hypersensitivity reaction, both basic science translational model.

Any further comments, Dr. Yustein or Dr. Fisher, before we proceed with the last question? Because I know patients, some people, members, have some planes to catch.

DR. YUSTEIN: No, but can I make a correction to something I said earlier?

DR. IGLESIA: Oh, of course.

DR. YUSTEIN: I just want to -- the eye in the sky kind of caught me on a mistake, so it goes back to the issue that Ms. Chauhan and I were discussing back and forth about patient informed consent, so we actually do have, apparently have the authority to put some restrictions on devices where we can insist that patients receive informed -- but that's by regulations and rule making, so that's not a quick process to take place, but we can do something like that. It's just a long, prolonged issue.

DR. IGLESIA: Elaine.

MS. BLYSKUN: Elaine Blyskun.

Question 6, the last one: Considering the information presented and discussed today, your own experience and knowledge of the device and the conditions for which it is used, as well as alternatives to its use, please discuss the overall benefit-risk profile for the Essure System. Within your discussion, please specifically describe the particular patient populations, if any, for whom the benefit-risk profile is acceptable (there is a reasonable assurance of safety and effectiveness) or the benefit-risk profile is unfavorable (device use is not recommended).

DR. IGLESIA: Who would like to lead that discussion? The ideal patient for the Essure implantation.

DR. JANIK: I can start.

DR. IGLESIA: Dr. Janik.

DR. JANIK: Grace Janik.

I think it's the patient who has -- is a high risk for laparoscopic procedures from

previous surgery, other health issues, obesity, so multiple reasons why laparoscopy would be a negative is the perfect patient for this type of a procedure, so I think that's the ideal patient.

DR. IGLESIA: Somebody who's failed the LARC method and has relative contraindication to general anesthesia.

DR. JANIK: Um-hum, exactly. And infavorable patients, that's the harder one to answer. I think we have suspicions that people who have history of hypersensitivity, potentially autoimmune issues would be ones that -- to think a little more deeply until we have more data.

DR. IGLESIA: Dr. Coddington.

DR. CODDINGTON: I think it was described in there about patients with pelvic inflammatory disease, prior surgery to the tube, would be, you know, a consideration. And we might say tube and uterus because there may be some alterations, as far as the uterus goes, if you've done a multiple myomectomy. The tube may not be right in the anatomic spot we think. So I would say surgery to --

DR. IGLESIA: Okay.

DR. CODDINGTON: -- uterus and tube. One could put as a possible is those that have had prior pelvic inflammatory disease. And the reason I say that is because there may be scar tissue in the fallopian tube that would make the application difficult.

DR. IGLESIA: Dr. Elser.

DR. ELSER: Denise Elser.

So any patient who desires permanent contraception, who's had a discussion of the

alternates, including LARC and including laparoscopic tubal, and chooses to have the device. But if the device, if you start the procedure and there's difficulty placing it, consider aborting early and not proceeding; do not force the procedure to go to its end.

DR. IGLESIA: Right.

Any other comments? And then I'll summarize.

(No response.)

DR. IGLESIA: Okay.

(Off microphone comment.)

DR. IGLESIA: No, I think we have to -- this is a closed discussion. So I'm going to --

MS. CHAUHAN: Cynthia Chauhan. Oh.

The risk-benefit, I like what you said. I would add to that. Risk-benefit should be discussed in great detail with patients prior to the procedure.

DR. IGLESIA: Okay.

Let's try and summarize and then -- so the question, in terms of the benefit-risk profile is acceptable, are patients who desire permanent contraception for whom a complete discussion of the risk and benefits as well as alternative forms of contraception has been done. And this may include patients who are at high risk to undergo general anesthesia or laparoscopy who may be obese and who have failed other reversible forms of contraception. However, for those who are unfavorable, these are patients who have a history of known hypersensitivity to something like nickel or metal who have chronic pelvic pain, perhaps, who have autoimmune disorders not otherwise specified or specified who have a history of pelvic inflammatory disease, either past or current, who have prior uterine

surgery that maybe have entered the uterine cavity like a myomectomy or tubal surgery, and in whom you do the procedure and it is not going straightforward and you have to abort, you know, that we need to make sure that we've had that discussion, that this may not be the right thing for you based on your anatomical -- or the situation at hand.

Denise.

DR. JANIK: Just one more quick comment. Vasectomy is also included in our list of options for a patient with a stable partner, and that anyone who's on hormonal contraceptives, part of the counseling is what may happen to your bleeding pattern or painful menses.

DR. IGLESIA: Oh, yes. The favorable patient has to be willing to be on a reliable form of birth control for the first 3 months, correct.

DR. SEIFER: And also if they have a history of DUB, maybe you might not want them to use this. I don't know.

DR. IGLESIA: Okay. History of abnormal uterine bleeding may be a relative contraindication as well.

UNIDENTIFIED SPEAKER: Undiagnosed.

DR. IGLESIA: Undiagnosed. Untreated, yeah.

Dr. Katz.

DR. KATZ: I'm reading this question and the two parts of it, and our mandate is to be responsive to what the question asks to the extent that we are able to. And the first part of the question involves what are the elements of the risk and benefit of Essure, and that's essentially what we've been talking about.

DR. IGLESIA: Yeah.

DR. KATZ: The second part of the question says the risk-benefit profile is acceptable for a subset of potential users, and it may be unfavorable. And I think it should be clear in our response to FDA and to the users of this device, in the audience, our participants and elsewhere, that this is how we're interpreting that statement because we're -- the adjective "acceptable" and "unfavorable" is in that question.

DR. IGLESIA: Correct. Would that -- with that caveat, would that change the discussion that we just had? Would that change anything?

DR. KATZ: That's my question.

DR. IGLESIA: Okay.

Dr. Yustein, Dr. Fisher, do you have other questions to the Panel about this? Has this question been answered satisfactorily?

(No audible response.)

DR. IGLESIA: Okay. So do you have something else to say?

(Pause.)

DR. IGLESIA: Well, then at this time the Panel would like -- we would like to thank the Panel. Is this it? Okay. At this time the Panel will hear summations, comments, or clarification from Bayer Healthcare. Bayer Healthcare, you have 5 minutes.

DR. ZAMPAGLIONE: Great, thank you.

So thank you very much, everybody. I would definitely like to thank Madam Chair, members of the committee, and truly all the participants. Really kudos to you guys for coming here to share your stories. We learned a lot, and we thank you for coming here.

As I stated in my opening comments, we really want to ensure the safe and appropriate use of all of our products. We don't deny that adverse events occur, and we make every attempt to mitigate them as best as possible. And we sympathize with any patient who has experienced an adverse event. We look forward to working with the FDA on these recommendations that you have made and on the next steps really to ensure that both physicians and patients really understand the benefits and risks of Essure, but not just Essure, all permanent methods of contraception and just contraception in general. The experience of today reinforces the diversity of needs and perspectives in the area of female reproductive health and argues for more options, not less.

Thank you very much.

DR. IGLESIA: Thank you.

At this time the Panel will hear summations, comments, or clarifications from the FDA. FDA, you have 5 minutes.

DR. FISHER: Thank you very much.

FDA is constantly faced with the challenge of trying to ensure that devices that show favorable benefit-risk profiles in controlled premarket clinical trials continue to perform with reasonable assurance of safety and effectiveness when they get out into routine clinical practice. And to try to accomplish this task, it's critical that FDA continues to listen to physicians, advocacy groups, professional societies, industry, advisory panels, to the patients themselves throughout the entire lifespan of the device. In addition, we review the required annual reports and the MDR reports.

Over the past few years, FDA has become aware of the growing number of safety

concerns with Essure that's been raised by women implanted with these devices and some of the physicians who have experience with the Essure device. We felt that it was important to hold this panel meeting to hear directly from the women implanted with the devices and to get the recommendation from the Panel based on the clinical and scientific data that's available. So the Panel members were asked to address a number of questions regarding the clinical events, additional data needs, labeling, and removal, as well as the benefit-risk associated with the Essure device.

In regards to clinical events, it was said that there are signals of concerns, but we don't seem to have a long-term patient management protocol. With persistent pain and late-developing pain, it's an issue, and we need to have an early patient intervention procedure, possibly a protocol change for patient management, which would include imaging after placement and even after confirmation. Bleeding alteration, they're a little bit more problematic, but -- because it's hard to determine if they're directly tied to the insert. But a regular and persistent bleeding warrants an interventional protocol on patient management.

Nickel sensitivity, wow. More data is needed. Could it be more than just nickel sensitivity? We've talked about hypersensitivity, autoimmune, immunocompromised patients. How do we define all these? Which patient populations overlay with other patient populations? Simple blood tests might be a good start, but is it going to be enough? There was talk about the possibility of a registry to address allergy and hypersensitivity concerns, and with pregnancy, there's some need for longer follow-up outcome data.

There was a comment made that we should be looking at bundling these procedures,

that patients that have access -- that need to have access to the entire process. If you can't have the device removed, then you shouldn't have it placed. And this also includes confirmation procedures.

We talked about risk mitigations and training physicians. The training should go beyond physician training. We need to have some type of -- there was a suggestion that we need to have some type of proficiency assessment. Patient counseling was stressed over and over to better define the rules for when you get an implant of a device and more rules on when you should not get an implant of a device. So we need to have better patient counseling to define these options.

We need to be able to clearly convey the real issues to the patients before they agree to the procedures, and there was a lot of talk about having an informed consent or a checklist for the patients and the physicians to discuss so that everybody's on board with what they're facing going into it.

With labeling, there was the comment that this should be considered a surgical procedure with a permanent implant. There's need for more information for the general risks and the issues associated with general hysteroscopy, and there needs to be something to capture the unknowns of this issue that we're calling nickel allergy or hypersensitivities. Patients need to be able to go into this procedure knowing a basic amount of information as to what the true risks and benefits of this device are.

The need for additional data, instead of another randomized control clinical trial, which would probably have to be too big and too expensive, there was a suggestion that we should try to get as much additional information from the studies that are already ongoing.

And there was a suggestion of a registry with close follow-up, that we might be able to use these to gather more useful postmarket data. We need to have patient evaluation on those who have had removals, and there's much need for ancillary tests for helping us get our heads around what these immunological issues are that we're faced with. And there was also discussion about more bench testing and clinical data that's needed for these autoimmune/immunocompromised/hypersensitivity issues.

When it comes to removal, we need to be able to provide information to physicians and patients on how these devices should be removed and how they can be safely removed. The physician that inserts the device may not be the one that removes it, so patients need to have access to both. There's a need for follow-up data on patients that have had these devices removed; if there's immediate pain, we should be talking about imaging.

For benefit-risk, we said that there are suitable populations, and these may include patients that are high risk for laparoscopic procedures, failed the LARC, but we have to have thoroughly informed patients if issues arise, and we should be aborting these procedures earlier and be discussing alternatives with the patients. Risk-benefit needs to thoroughly be discussed before the procedures are initiated.

Not suitable patients. There's a lot of questions about these metal allergies, hypersensitivities; until there's more data available, I think that we need to consider these patients carefully. We also said non-suitable patients may be those who have had prior uterine surgery that might complicate the insert itself. And patients need to be able to go on alternate birth control for at least 3 months.

So where do we go from here? I think that, and I hope that everyone understands,

that we saw the actions that FDA has already taken, and I'm talking about some of the labeling changes, some of the meetings that we've had with the patients and the advocacy groups prior to this, and even this panel meeting itself, that everyone realizes that FDA considers this to be a high priority issue. So, moving forward, the Agency will consider all the comments as well as the scientific presentations, the public testimony, the Panel recommendations in determining our next steps. And, of course, any next steps will be publicly communicated.

I'd like to remind everyone that the docket is still open until October 24th, so for those patients who did not have an opportunity to present today, FDA would like to remind everyone that the docket remains open, and we encourage members of the public to post their comments to the public docket announcing this meeting until the comment period closes.

I would like to thank the Panel members for providing their input; for the company, Bayer, for your presentations today; the professional societies and the advocacy groups for providing their comments. Our primary concern continues to be the safety and well-being of the patients, and with that, I would like to thank the patients and their families and the physicians who traveled to our agency today to share their personal stories or professional experiences. Many of you came today, and we really appreciate your attendance at this meeting. You traveled a large distance, and it's not easy getting up in front of a large crowd and presenting before a panel. It can be difficult. But I want you to know that to us, it's very important. So thank you very much.

And with that, Madam Chair, that's all I have.

DR. IGLESIA: I would like to thank the Panel, FDA, Bayer Healthcare, and all Open Public Hearing speakers for your contributions to today's meeting.

Dr. Yustein, do you have any final comments?

(No audible response.)

DR. IGLESIA: So the September 24, 2015 meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee is thus adjourned. Thank you very much, and good evening.

(Whereupon, at 8:08 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

OBSTETRICS AND GYNECOLOGY DEVICES PANEL

September 24, 2015

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter